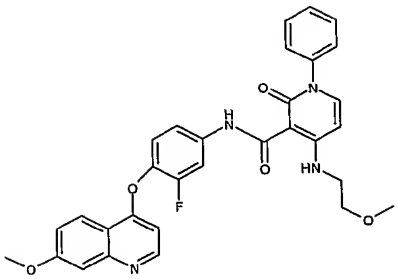
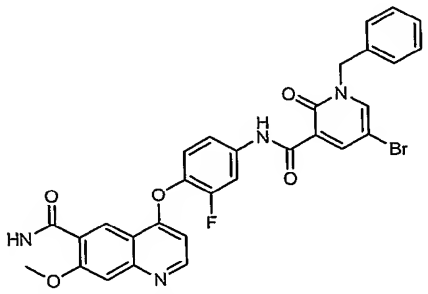
Example 214



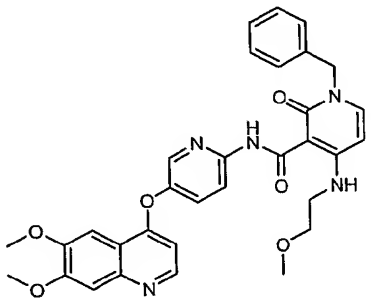
N-(3-fluoro-4-(7-methoxyquinolin-4-yloxy)phenyl)-4-(2-methoxyethylamino)-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamide: MS (ESI pos. ion) m/z 555 (MH+). Calc'd exact mass for $C_{31}H_{27}FN_4O_5$ 554

Example 215



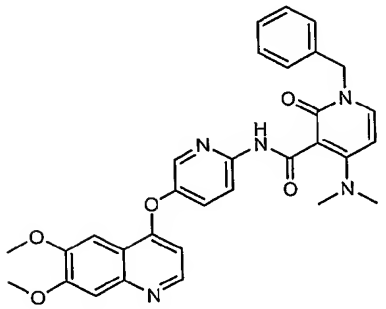
N-(4-((6,7-bis(methyloxy)-4-quinolinyl)oxy)-3-fluorophenyl)-1-cyclopentyl-6-oxo-5-(2-oxo-1-pyrrolidinyl)-1,6-dihydro-3-pyridinecarboxamide: MS (ESI pos. ion) m/z: 617 (MH+). Calc'd exact mass for $C_{30}H_{21}BrFN_4O_5$: 616

Example 216



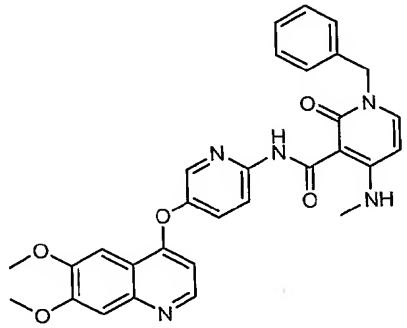
1-benzyl-N-(5-(6,7-dimethoxyquinolin-4-yloxy)pyridin-2-yl)-4-(2-methoxyethylamino)-2-oxo-1,2-dihydropyridine-3-carboxamide: MS (ESI pos. ion) m/z: 582 (MH+). Calc'd exact mass for $C_{32}H_{31}N_5O_6$: 581. 1H NMR (400 MHz, DMSO-d_6) 13.45 (s, 1 H) 10.58 (s, 1 H) 8.49 (d, *J*=5.13 Hz, 1 H) 8.33 (dd, *J*=5.90, 2.82 Hz, 2 H) 7.89 (d, *J*=7.69 Hz, 1 H) 7.79 (dd, *J*=9.10, 2.69 Hz, 1 H) 7.54 (s, 1 H) 7.41 (s, 1 H) 7.26 - 7.39 (m, 5 H) 6.52 (d, *J*=5.13 Hz, 1 H) 6.26 (d, *J*=7.69 Hz, 1 H) 5.10 (s, 2 H) 3.94 (d, *J*=3.33 Hz, 6 H) 3.48 - 3.59 (m, 4 H) 3.32 (s, 3 H)

Example 217



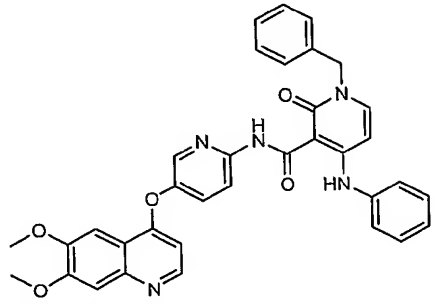
1-benzyl-N-(5-(6,7-dimethoxyquinolin-4-yloxy)pyridin-2-yl)-4-(dimethylamino)-2-oxo-1,2-dihydropyridine-3-carboxamide: MS (ESI pos. ion) m/z: 552 (MH+). Calc'd exact mass for $C_{31}H_{29}N_5O_5$: 551.

Example 218



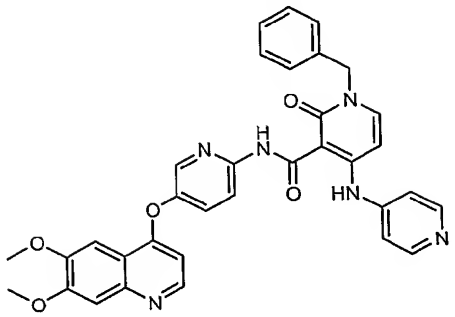
1-benzyl-N-(5-(6,7-dimethoxyquinolin-4-yloxy)pyridin-2-yl)-4-(methylamino)-2-oxo-1,2-dihydropyridine-3-carboxamide: MS (ESI pos. ion) m/z: 538 (MH+). Calc'd exact mass for $C_{30}H_{27}N_5O_5$: 537.

Example 219



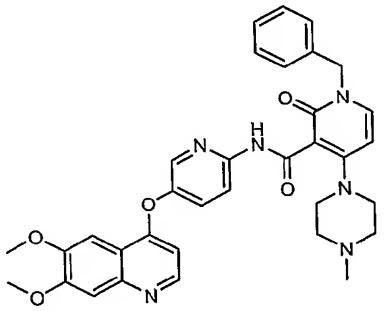
1-benzyl-N-(5-(6,7-dimethoxyquinolin-4-yloxy)pyridin-2-yl)-2-oxo-4-(phenylamino)-1,2-dihydropyridine-3-carboxamide: MS (ESI pos. ion) m/z: 600 (MH+). Calc'd exact mass for $C_{35}H_{29}N_5O_5$: 599.

Example 220



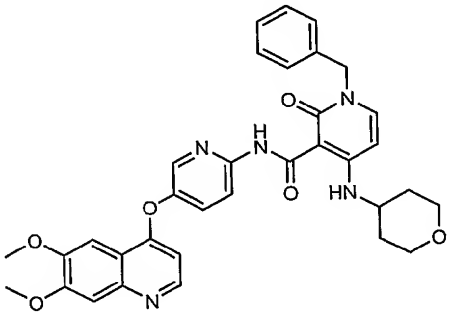
1-benzyl-N-(5-(6,7-dimethoxyquinolin-4-yloxy)pyridin-2-yl)-2-oxo-4-(pyridin-4-ylamino)-1,2-dihydropyridine-3-carboxamide: MS (ESI pos. ion) m/z: 601 (MH+). Calc'd exact mass for $C_{34}H_{28}N_6O_5$: 600. 1H NMR (400 MHz, DMSO-d_6) 13.48 (s, 1 H) 12.46 (s, 1 H) 8.45 - 8.57 (m, 3 H) 8.34 (d, *J*=12.05 Hz, 2 H) 8.02 (d, 1 H) 7.83 (s, 1 H) 7.52 (s, 1 H) 7.32 - 7.42 (m, 7 H) 6.50 - 6.60 (m, 2 H) 3.93 (s, 3 H) 3.92 (s, 3 H)

Example 221



1-benzyl-N-(5-(6,7-dimethoxyquinolin-4-yloxy)pyridin-2-yl)-4-(4-methylpiperazin-1-yl)-2-oxo-1,2-dihydropyridine-3-carboxamide: MS (ESI pos. ion) m/z: 607 (MH+). Calc'd exact mass for $C_{34}H_{34}N_6O_5$: 606.

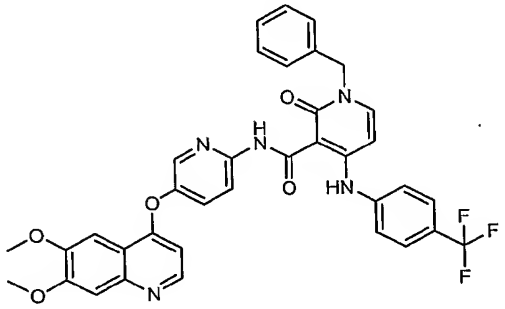
Example 222



1-benzyl-N-(5-(6,7-dimethoxyquinolin-4-yloxy)pyridin-2-yl)-2-oxo-4-(tetrahydro-2H-pyran-4-ylamino)-1,2-dihydropyridine-3-carboxamide: MS (ESI pos. ion) m/z: 608 (MH+). Calc'd exact mass for $C_{34}H_{33}N_5O_6$: 607. 1H NMR (400 MHz, DMSO-d_6) 13.47 (s, 1 H) 10.66 (d, *J*=7.58 Hz, 2 H) 8.50 (d, *J*=5.18 Hz, 1 H) 8.31 - 8.36 (m, 1 H) 7.89 (d, *J*=7.83 Hz,

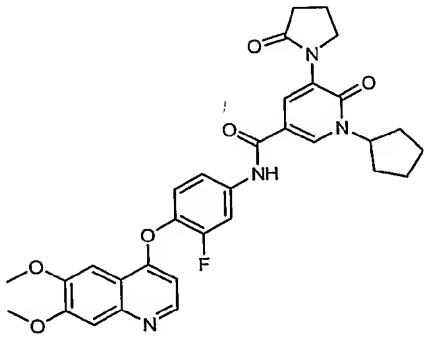
1 H) 7.78 (dd, *J*=8.97, 3.03 Hz, 1 H) 7.55 (s, 1 H) 7.42 (s, 1 H) 7.26 - 7.40 (m, 5 H) 6.53 (d, *J*=5.18 Hz, 1 H) 6.36 (d, *J*=7.83 Hz, 1 H) 5.11 (s, 2 H) 3.95 (d, *J*=4.04 Hz, 6 H) 3.86 (d, *J*=11.49 Hz, 3 H) 3.45 - 3.55 (m, 3 H) 1.89 - 1.99 (m, 2 H) 1.44 - 1.57 (m, 2 H)

Example 223



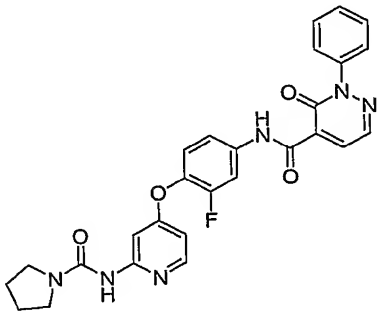
1-benzyl-N-(5-(6,7-dimethoxyquinolin-4-yloxy)pyridin-2-yl)-2-oxo-4-(4-(trifluoromethyl) phenylamino)-1,2-dihydropyridine-3-carboxamide: MS (ESI pos. ion) m/z: 668 (MH+). Calc'd exact mass for $C_{36}H_{28}F_3N_5O_5$: 667. 1H NMR (400 MHz, DMSO-d_6) □ ppm 13.59 (s, 2 H) 12.42 (s, 1 H) 8.82 (d, *J*=6.44 Hz, 1 H) 8.49 (d, *J*=2.91 Hz, 1 H) 8.44 (d, *J*=9.09 Hz, 1 H) 7.77 (s, 1 H) 7.29 - 7.42 (m, 5 H) 7.00 (d, *J*=6.44 Hz, 1 H) 5.18 (s, 2 H) 4.05 (s, 3 H) 4.03 (s, 3 H)

Example 224



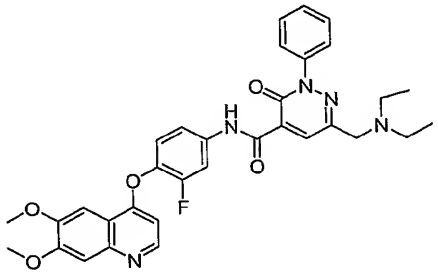
1-cyclopentyl-N-(4-(6,7-dimethoxyquinolin-4-yloxy)-3-fluorophenyl)-6-oxo-5-(2-oxopyrrolidin-1-yl)-1,6-dihydropyridine-3-carboxamide: MS (ESI pos. ion) m/z: 587 (MH+). Calc'd exact mass for $C_{32}H_{31}FN_4O_6$: 586.

Example 225



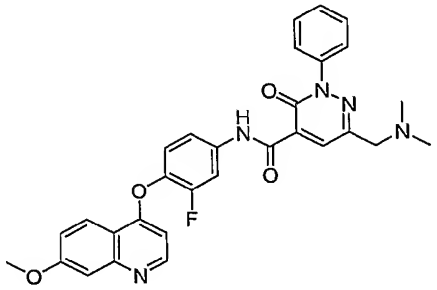
N-(3-fluoro-4-(2-(pyrrolidine-1-carboxamido)pyridin-4-yloxy)phenyl)-3-oxo-2-phenyl-2,3-dihydropyridazine-4-carboxamide: MS (ESI pos. ion) m/z: 515 (MH+). Calc'd exact mass for $C_{27}H_{23}FN_6O_4$: 514. ^{1}HNMR (300 MHz, $CDCl_3$): 1.23 (s, 1H), 1.52 (s, 4H), 2.98-3.08 (m, 5H), 6.10 (s, 1H), 6.11 (d, J=4.11 Hz, 1H), 6.61 (s, 1H), 6.73 (t, J=8.61 Hz, 1H), 6.84 (s, 1H), 6.91 (s, 1H), 7.09 (d, J=6.65 Hz, 1H), 7.15 (q, J=7.96 Hz, 2H), 7.29 (s, 1H), 7.49 (d, J=12.13 Hz, 1H), 7.61 (d, J=5.67 Hz, 1H), 7.80 (d, J=3.91 Hz, 1H), 7.97 (d, J=4.11 Hz, 1H), 11.39 (s, 1H).

Example 226



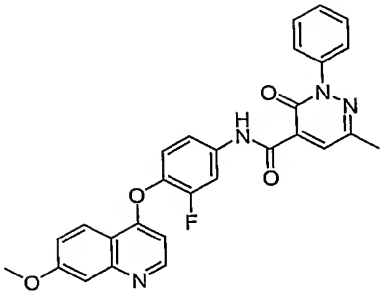
6-((diethylamino)methyl)-N-(4-(6,7-dimethoxyquinolin-4-yloxy)-3-fluorophenyl)-3-oxo-2-phenyl-2,3-dihydropyridazine-4-carboxamide: MS (ESI pos. ion) m/z: 598 (MH+). Calc'd exact mass for $C_{33}H_{32}FN_5O_5$: 597. ^{1}HNMR (300 MHz, $CDCl_3$): 11.99 (s, 1H), 8.61 (s, 2H), 8.04 (s, 1H), 7.82 (s, 1H), 7.57 (m, 4H), 7.26 (s, 3H), 6.61 (s, 1H), 4.10 (d, J=6.1 Hz, 9H), 3.82 (s, 2H), 3.16 (s, 1H), 2.79 (s, 4H), 1.81 (s, 1H), 1.27 (s, 1H).

Example 227



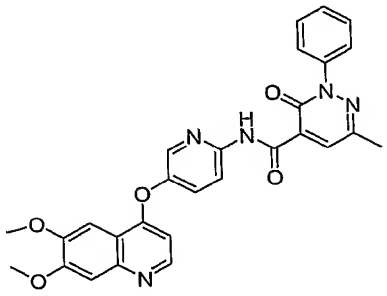
6-((dimethylamino)methyl)-N-(3-fluoro-4-(7-methoxyquinolin-4-yloxy)phenyl)-3-oxo-2-phenyl-2,3-dihydropyridazine-4-carboxamide: MS (ESI pos. ion) m/z: 540 (MH+). Calc'd exact mass for $C_{30}H_{26}FN_5O_4$: 539. ^{1}HNMR (300 MHz, $CDCl_3$): 1.71 (s, 1H), 1.75 (ddd, J=6.4, 3.5, 3.3 Hz, 3H), 2.30 (s, 2H), 3.03-3.13 (m, J=6.5, 3.6, 3.3, 3.3, Hz, 3H), 3.51 (s, 1H), 3.93 (s, 2H), 6.70-6.75 (m, 2H), 7.20 (m, 2H), 7.33-7.54 (m, 6H), 7.80 (d, 1H), 8.45 (d, 1H), 8.52 (s, 1H), 11.85 (s, 1H).

Example 228



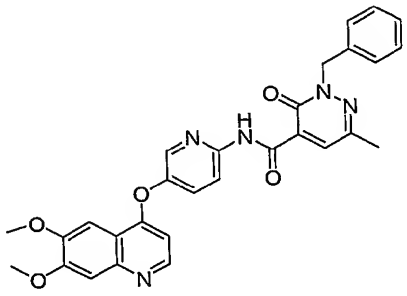
N-(3-fluoro-4-(7-methoxyquinolin-4-yloxy)phenyl)-6-methyl-3-oxo-2-phenyl-2,3-dihydropyridazine-4-carboxamide: MS (ESI pos. ion) m/z: 497 (MH+). Calc'd exact mass for $C_{28}H_{21}FN_4O_4$: 496. ^{1}HNMR (300 MHz, $CDCl_3$): 2.54 (s, 3H), 3.96 (s, 4H), 6.40 (s, 1H), 7.24 (s, 2H), 7.40 (s, 2H), 7.55 (s, 4H), 7.96 (s, 1H), 8.29 (s, 2H), 8.59 (s, 1H), 12.01 (s, 1H).

Example 229



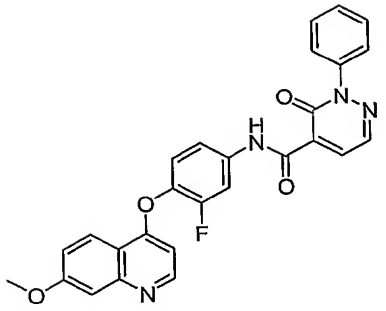
N-(5-(6,7-dimethoxyquinolin-4-yloxy)pyridin-2-yl)-6-methyl-3-oxo-2-phenyl-2,3-dihydropyridazine-4-carboxamide: MS (ESI pos. ion) m/z: 510 (MH+). Calc'd exact mass for $C_{28}H_{23}N_5O_5$: 509. ^{1}HNMR (300 MHz, $CDCl_3$): 2.55 (s, 3H), 4.06 (d, J=1.2 Hz, 6H), 6.49 (d, J=5.3 Hz, 1H), 6.82 (s, 1H), 7.45-7.64 (m, 7H), 8.29-8.33 (m, 1H), 8.46 (d, J=8.9 Hz, 1H), 8.52 (d, J=5.3 Hz, 1H), 12.37 (s, 1H).

Example 230



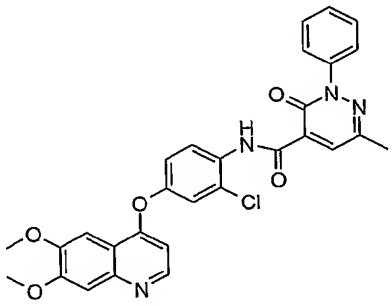
2-benzyl-N-(5-(6,7-dimethoxyquinolin-4-yloxy)pyridin-2-yl)-6-methyl-3-oxo-2,3-dihydropyridazine-4-carboxamide: MS (ESI pos. ion) m/z: 524 (MH+). Calc'd exact mass for $C_{29}H_{25}N_5O_5$: 523. ^{1}HNMR (300 MHz, $CDCl_3$): 2.48 (s, 3H), 4.06 (s, 6H), 5.30 (s, 2H), 5.42 (s, 2H), 6.46 (d, J=5.3 Hz, 1H), 7.35 (d, J=6.7 Hz, 2H), 7.43-7.61 (m, 3H), 8.17 (s, 1H), 8.34 (s, 1H), 8.44 (d, J=8.9 Hz, 1H), 8.52 (d, J=5.1 Hz, 1H), 12.50 (s, 1H).

Example 231



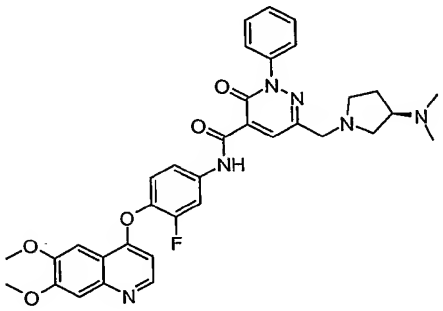
N-(3-fluoro-4-(7-methoxyquinolin-4-yloxy)phenyl)-3-oxo-2-phenyl-2,3-dihydropyridazine -4-carboxamide: MS (ESI pos. ion) m/z: 483 (MH+). Calc'd exact mass for $C_{27}H_{19}FN_4O_4$: 482. ^{1}HNMR (300 MHz, $CDCl_3$): 3.97 (s, 3H), 5.30 (s, 1H), 6.41 (d, J=4.1 Hz, 1H), 7.19-7.28 (m, 3H), 7.58 (s, 3H), 7.96 (d, J=11.8 Hz, 1H), 8.24 (d, J=2.9 Hz, 2H), 8.28 (s, 1H), 8.42 (d, J=3.9 Hz, 1H), 8.60 (d, J=5.0 Hz, 1H), 11.89 (s, 1H).

Example 232



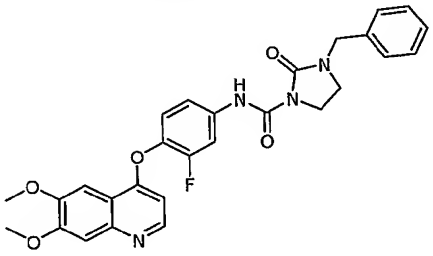
N-(2-chloro-4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-6-methyl-3-oxo-2-phenyl-2,3-dihydropyridazine-4-carboxamide: MS (ESI pos. ion) m/z: 543 (MH+). Calc'd exact mass for $C_{29}H_{23}ClN_4O_5$ 542. 1H NMR (400 MHz, $CDCl_3$) 12.24 (s, 1 H), 8.68 (d, *J*=9.28 Hz, 1 H,), 8.53 (d, *J*=5.37 Hz, 1 H), 8.32 (s, 1 H), 7.73-7.40 (m, 7 H), 7.30 (s, 1H), 7.17 (d, J=7.81, 1H), 6.57 (d, *J*=4.40 Hz, 1 H,), 4.07 (s, 3 H), 4.05 (s, 3 H), 2.54 (s, 3 H,)

Example 233



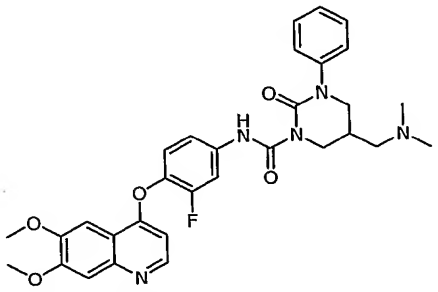
(*R*)-N-(4-(6,7-dimethoxyquinolin-4-yloxy)-3-fluorophenyl)-6-((3-(dimethylamino) pyrrolidin-1-yl)methyl)-3-oxo-2-phenyl-2,3-dihydropyridazine-4-carboxamide: MS (ESI pos. ion) m/z 639 (MH+). Calc'd exact mass for $C_{35}H_{35}FN_6O_5$ 638.

Example 234



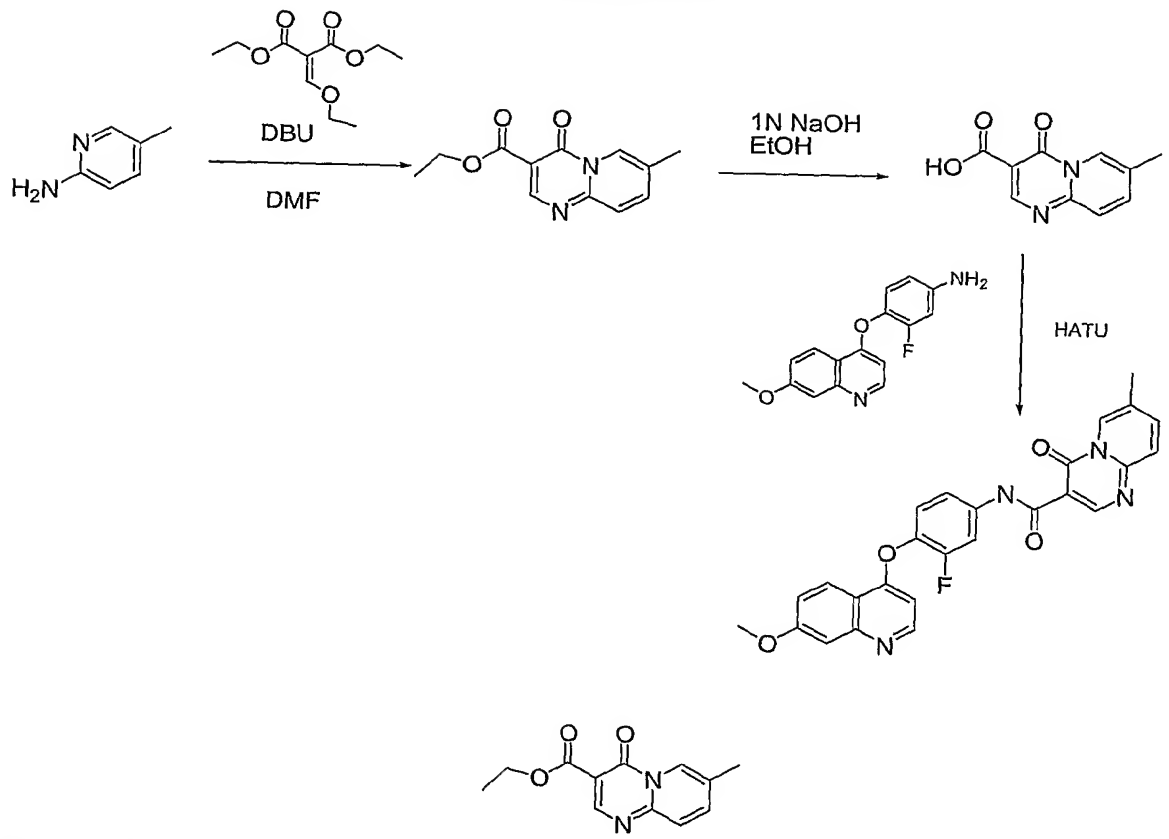
3-benzyl-N-(4-(6,7-dimethoxyquinolin-4-yloxy)-3-fluorophenyl)-2-oxoimidazolidine-1-carboxamide: MS (ESI pos. ion) m/z: 517 (MH+). Calc'd exact mass for $C_{28}H_{25}FN_4O_5$: 516.

Example 235

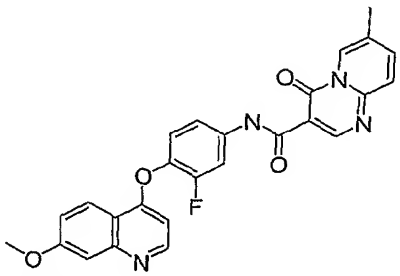


N-(4-(6,7-dimethoxyquinolin-4-yloxy)-3-fluorophenyl)-5-((dimethylamino)methyl)-2-oxo-3-phenyl-tetrahydropyrimidine-1(2H)-carboxamide: MS (ESI pos. ion) m/z: 574 (MH+). Calc'd exact mass for $C_{31}H_{32}FN_5O_5$: 573.

Example 236



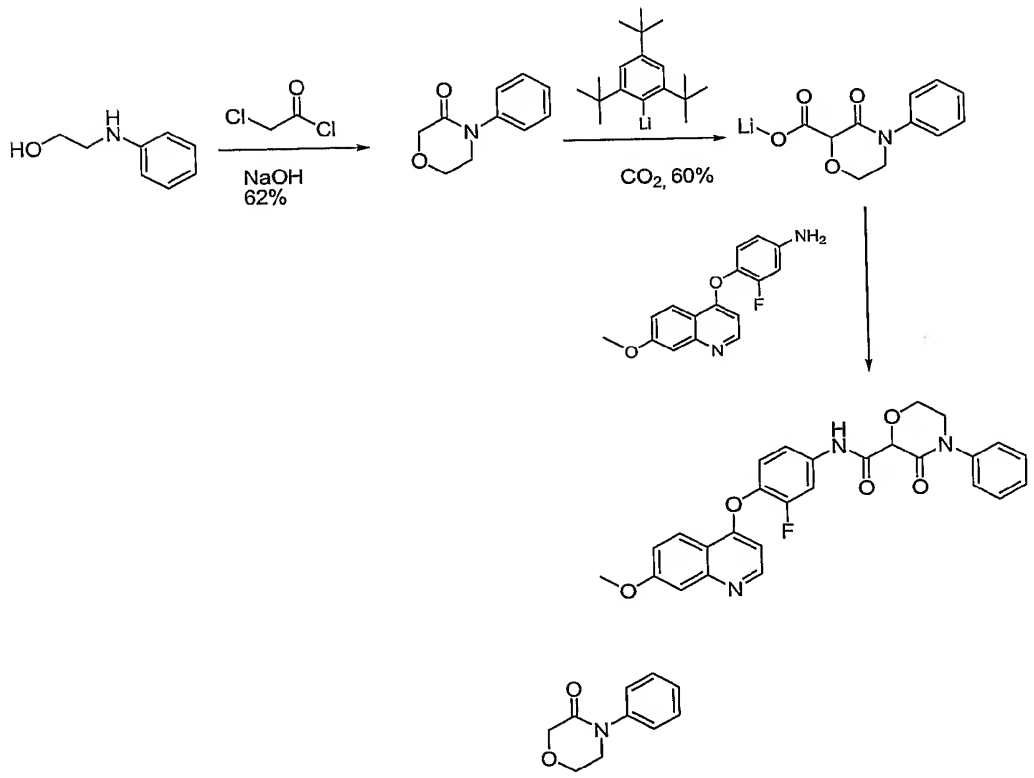
Step 1: Ethyl 7-methyl-4-oxo-4H-pyrido[1,2-a]pyrimidine-3-carboxylate. A mixture of diethyl 2-(ethoxymethylene)malonate (0.60 g, 3 mmol), 5-methylpyridin-2-amine (0.20 g, 2 mmol), DBU (0.1 ml, 0.9 mmol) in acetonitrile (2 g, 49 mmol) was heated under Microwave (CEM) at 150 °C (150 W) for 20 min. The resultant was diluted with dichloromthane and water, and the organic layer was dried over sodium sulfate. The organic solution was concentrated, and the residue was crystallized in dichloromethane and diethyl ether to give the title compound as a pale yellow solid (0.25 g, 58 %): MS (ESI pos. ion) m/z: 233 (MH+). Calc'd exact mass for $C_{12}H_{12}N_2O_3$: 232.



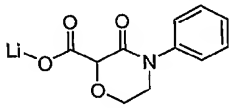
Steps 2 and 3: N-(3-fluoro-4-(7-methoxyquinolin-4-yloxy)phenyl)-7-methyl-4-oxo-4H-pyrido[1,2-a]pyrimidine-3-carboxamide. To a suspension of ethyl 7-methyl-4-oxo-4H-pyrido[1,2-a]pyrimidine-3-carboxylate (0.11 g, 0.47 mmol) in ethanol was added 1 N NaOH

solution (3 mL, 3mmol) at RT. The reaction mixture was stirred for 16 at RT. The resultant was concentrated, and the residue was diluted with water. The aqueous solution was washed with diethyl ether and then acidified with 2N HCl solution and extracted with dichloromethane. The organic solution was dried over magnesium sulfate and concentrated to give a yellow solid (0.090 g, 93%): MS (ESI pos. ion) m/z: 205 (MH+). Calc'd exact mass for $C_{10}H_8N_2O_3$: 204. A mixture of 3-fluoro-4-(7-methoxyquinolin-4-yloxy)benzenamine (0.08 g, 0.3 mmol), 7-methyl-4-oxo-4H-pyrido[1,2-a]pyrimidine-3-carboxylic acid (0.08 g, 0.4 mmol), HATU (0.4 g, 0.8 mmol) in dichlormethane was stirred for 16 h. Then, the mixture was diluted with dichloromethane and aq. NaHCO3 solution. The organic layer was separated, dried over Na2SO4 and concentrated. The residue was purified by ISCO (0-5 % MeOH in EtOAc) to give the title compound as a yellow solid (0.032 g, 24 %): MS (ESI pos. ion) m/z: 471 (MH+), Calc'd exact mass for $C_{26}H_{19}FN_4O_4$: 470; ^{1}HNMR (400 MHz, $CDCl_3$): 11.4 (s, 1H), 9.4 (s, 1H), 9.1 (s, 1H), 8.6 (d, J= 6 Hz, 1H), 8.3 (d, J= 9 Hz, 1H), 8.0 (dd, J= 3, 12 Hz, 1H), 7.9 (m, 2H), 7.5 (m, 1H), 7.4 (d, J- 3 Hz, 1H), 7.0-7.3 (m, 2H), 6.4 (d, J= 3 Hz, 1H), 3.98 (s, 3H), 2.57 (s, 3H).

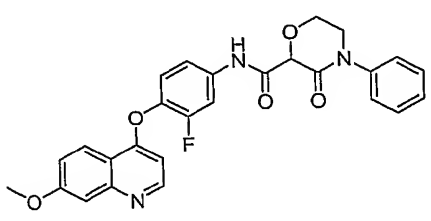
Example 237



Step 1: 4-Phenylmorpholin-3-one. A 250-mL flask was charged with 2-anilinoethanol (9.17 ml, 73.2 mmol), 9 mL dry EtOH, an overhead stirrer, a calibrated pH probe, and 27 mL water. An addition funnel was charged with 10 N sodium hydroxide solution (45.4 ml, 454 mmol). The solution was heated to 41 °C, and treated with chloracetyl chloride (17.5 ml, 220 mmol) *via* a syringe pump over 1 h. The sodium hydroxide solution was simultaneously added to the stirring solution so that the pH was maintained between 12 and 12.5. After the addition was complete, the solution was cooled to 0 °C and stirred for 1 h. The solids were collected and washed with water (2 X 60 mL cold water). The solids were dried at 50 °C at 0.2 mm Hg for 36 h to afford 4-phenylmorpholin-3-one (8.10 g, 62.5% yield). ^{1}H NMR (400 MHz, CHLOROFORM-d) 3.75 - 3.80 (m, 2 H) 4.02 - 4.06 (m, 2 H) 4.35 (s, 2 H) 7.27 - 7.36 (m, 3 H) 7.39 - 7.46 (m, 2 H). ^{13}C NMR (101 MHz, CHLOROFORM-d) 49.69 (s, 1 C) 64.14 (s, 1 C) 68.57 (s, 1 C) 125.48 (s, 2 C) 127.15 (s, 1 C) 129.30 (s, 2 C) 141.31 (s, 1 C) 166.59 (s, 1 C).

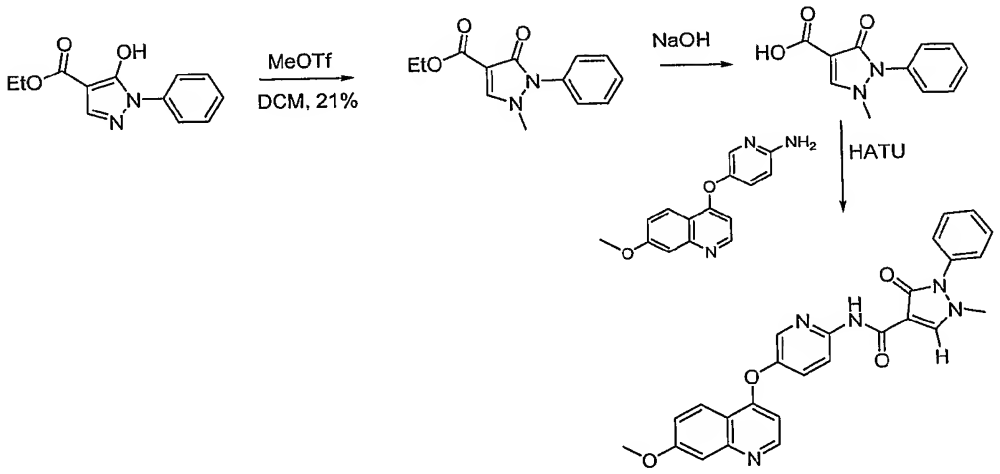


Step 2: Lithium 3-oxo-4-phenylmorpholine-2-carboxylate. A dry 100 mL Schlenk-type flask was fitted with a nitrogen/vacuum line and charged with 2-bromo-1,3,5-tri-tert-butylbenzene (0.521 g, 1.601 mmol), 20 mL dry THF, and a stirbar. The solution was cooled to -78 °C and treated with 2.5M butyllithium (0.582 ml, 1.456 mmol). The reaction was stirred for 15min and treated with 4-phenylmorpholin-3-one (0.258 g, 1.456 mmol) dissolved in 2 mL dry THF dropwise over 5 min. The reaction was stirred for 2 h at -78 °C. The side arm compartment of the Schlenk-type flask was charged with ~1g dry ice. The system was sealed, and the dry ice was allowed to sublime into the solution. After 30 min, a nitrogen needle was fitted to the flask, and a solid was noted in the solution. The cooling bath was removed, which caused the solids to bubble (presumably dry ice). The solution was allowed to warm to RT overnight. The solution was diluted with 40 mL water and extracted with dichloromethane (2x10 mL). The water was concentrated *in vacuo* and dried at 60 °C and 0.15 mmHg to afford lithium 3-oxo-4-phenylmorpholine-2-carboxylate (0.200 g, 60.5% yield). ^{1}H NMR (400 MHz, D_2O) 3.72 (t, J=5.23 Hz, 2 H), 3.99 (dt, J=12.10, 5.29 Hz, 1 H), 4.08 (dt, J=12.15, 5.22 Hz, 1 H), 4.61 (s, 1 H), 7.24 - 7.28 (m, 2 H), 7.32 (tt, 1 H), 7.38 - 7.44 (m, 2 H).

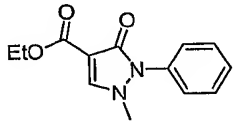


Step 3: N-(3-Fluoro-4-(7-methoxyquinolin-4-yloxy)phenyl)-3-oxo-4-phenylmorpholine-2-carboxamide. A dry, 10 mL schlenk-type flask was charged with a stirbar, lithium 3-oxo-4-phenylmorpholine-2-carboxylate (0.096 g, 0.42 mmol), triethylammonium hydrochloride (0.058 g, 0.42 mmol), 3*H*-[1,2,3]triazolo[4,5-b]pyridin-3-ol (0.072 g, 0.53 mmol), and evacuated. The flask was back-filled with nitrogen and treated with 2 mL dry THF and 1 mL dry NMP. To the stirring solution was added Si-DCC (0.55 g, 0.53 mmol) followed by3-fluoro-4-(7-methoxyquinolin-4-yloxy)benzenamine (0.100 g, 0.35 mmol). The reaction was stirred for 3 d at RT, and then 60 °C for 24 h. The slurry was filtered through a 0.22 μm frit, and the THF removed. The crude was purified by HPLC (Waters Spherisorb S5 column (PN PSS830195, 20 X 250 mm, 60 Å pore, 5 μm particle size)) to afford the title compound (0.026 g, 15.2% yield) ^{1}H NMR (400 MHz, Chloroform-d) 3.74 (ddd, J=12.32, 3.72, 3.52 Hz, 1 H), 3.95 - 4.03 (m, 4 H), 4.23 (dt, J=12.42, 3.91 Hz, 1 H), 4.27 - 4.38 (m, 1 H), 5.06 (s, 1 H), 6.37 (dd, J=5.23, 1.12 Hz, 1 H), 7.20 (t, J=8.56 Hz, 1 H), 7.24 (dd, J=9.15, 2.49 Hz, 1 H), 7.27 (ddd, J=8.83, 2.47, 1.12 Hz, 1 H), 7.32 - 7.41 (m, 3 H), 7.43 (d, J=2.45 Hz, 1 H), 7.46 - 7.51 (m, 2 H), 7.81 (dd, J=12.03, 2.35 Hz, 1 H), 8.26 (d, J=9.19 Hz, 1 H), 8.59 (d, J=5.18 Hz, 1 H), 9.66 (br. s., 1 H). MS (ESI pos. ion) m/z = 488, calc'd for $C_{27}H_{22}FN_3O_5$ 487.

Example 238

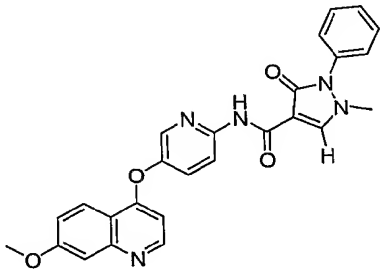


N-(5-(7-methoxyquinolin-4-yloxy)pyridin-2-yl)-1-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide



Step 1: Ethyl 1-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxylate. To a solution of ethyl 3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxylate (1000 mg, 5.0

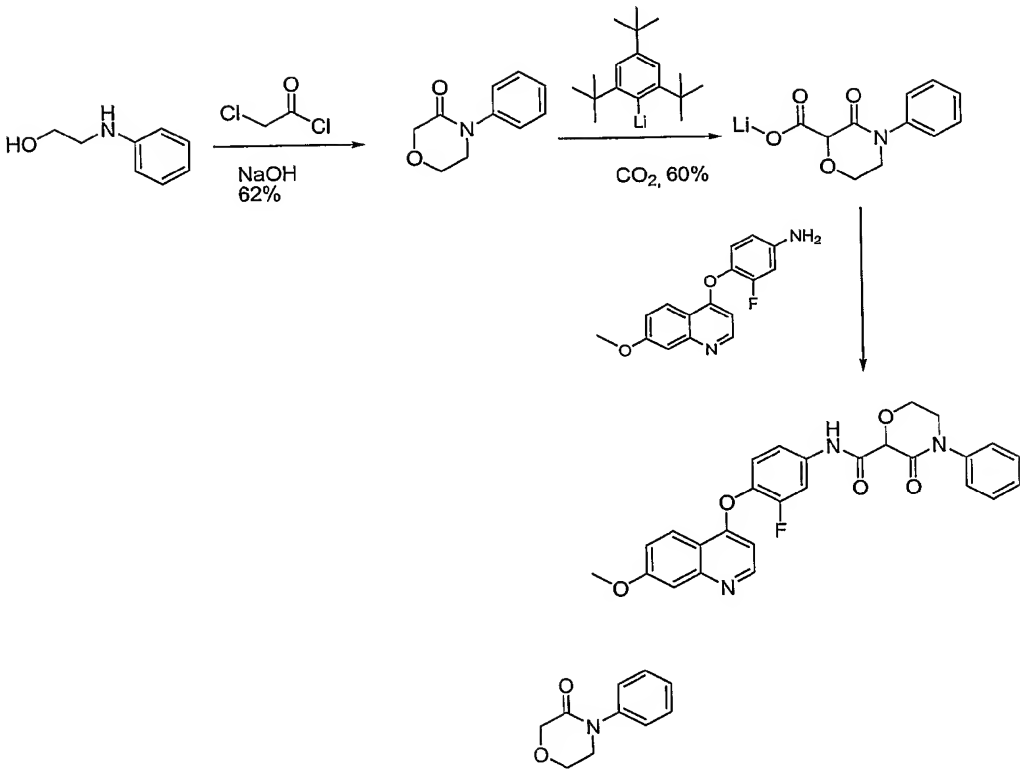
mmol) in dichloromethane (10 mL) was added methyl trifluoromethanesulfonate (1200 mg, 7.3 mmol). The red solution was stirred at room temperature. After 14 h, the mixture was partitioned between dichloromethane and $NaHCO_3$ (sat). The aqueous was extracted with dichloromethane (2x). The combined organic was dried over Na_2SO_4, concentrated and purified on silica. The product was triturated with EtOAc-hexane-$CHCl_3$ to give the pure product as crystals (260 mg, 21%). Calc'd for $C_{12}H_{12}N_2O_3$, 232.08; MS (ESI pos. ion) m/z: 233 (MH+). ^1H NMR (400 MHz, CHLOROFORM-d): 1.36 (t, J=7.04 Hz, 3 H), 3.39 (s, 3 H), 4.32 (q, J=7.17 Hz, 2 H), 7.32 (d, J=7.43 Hz, 2 H), 7.42 (t, J=7.34 Hz, 1 H), 7.50 (t, J=7.73 Hz, 2 H), 7.99 (s, 1 H).



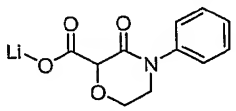
Step 2: N-(5-(7-methoxyquinolin-4-yloxy)pyridin-2-yl)-1-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide. A solution of ethyl 1-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxylate (260 mg, 1056 µmol) in MeOH was treated with NaOH (1000 µl, 5000 µmol) in H_2O (3 mL). The mixture was heated to 60 °C for 30 min and then cooled to room temperature. Then, the mixture was neutralized with aq. HCl (5 N, 1.1 mL) and concentrated to dryness. The residue was further dried with (azeotrope distillation with toluene, 3 x 5 mL). The resulting carboxylic acid was mixed with 5-(7-methoxyquinolin-4-yloxy)pyridin-2-amine (282 mg, 1054 µmol), Et_3N (500 µl, 3587 µmol), and HATU (401 mg, 1054 µmol) in DMF (4 mL) - dichloromethane (5 mL) and was stirred at 60 °C for 2 h. Upon cooling to room temperature, the mixture was diluted with EtOAc containing 10% MeOH (30 mL) and washed with H_2O. The organic layer was dried over Na_2SO_4, concentrated, and eluded on silica (1-10% 2N NH_3-MeOH in $CHCl_3$). The product was further purified on preparative HPLC to afford a white powder (100 mg, 20%).

Calc'd for $C_{26}H_{21}N_5O_4$: 467.16; MS (ESI pos. ion) m/z: 468 (MH+). ^1H NMR (400 MHz, DMSO-d_6) 3.49 (s, 3 H) 3.95 (s, 3 H) 6.55 (d, J 5.1, 1 H) 7.30 (dd, J 2.0, 9.0, 1 H) 7.42 (s, 1 H) 7.59 (s, 17 H) 7.50- 7.60 (m, 5 H), 7.84 (dd, J 2.8, 9.2, 1H), 8.22 (d, J 9.2, 1H), 8.34 - 8.38 (m, 2 H) 8.62 (d, J 5.3, 1 H) 8.69 (s, 1 H) 10.86 (s, 1 H).

Example 239

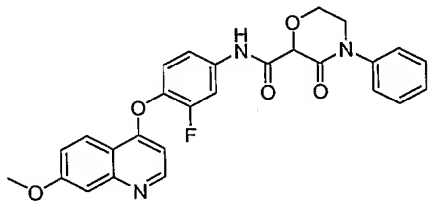


Step 1: 4-Phenylmorpholin-3-one. A 250-mL flask was charged with 2-anilinoethanol (9.17 ml, 73.2 mmol), 9 mL dry EtOH, an overhead stirrer, a calibrated pH probe, and 27 mL water. An addition funnel was charged with 10 N sodium hydroxide solution (45.4 ml, 454 mmol). The solution was heated to 41 °C, and treated with chloracetyl chloride (17.5 ml, 220 mmol) *via* a syringe pump over 1 h. The sodium hydroxide solution was simultaneously added to the stirring solution so that the pH was maintained between 12 and 12.5. After the addition was complete, the solution was cooled to 0 °C and stirred for 1 h. The solids were collected and washed with water (2 X 60 mL cold water). The solids were dried at 50 °C at 0.2 mm Hg for 36 h to afford 4-phenylmorpholin-3-one (8.10 g, 62.5% yield). ^{1}H NMR (400 MHz, CHLOROFORM-d) 3.75 - 3.80 (m, 2 H) 4.02 - 4.06 (m, 2 H) 4.35 (s, 2 H) 7.27 - 7.36 (m, 3 H) 7.39 - 7.46 (m, 2 H). ^{13}C NMR (101 MHz, CHLOROFORM-d) 49.69 (s, 1 C) 64.14 (s, 1 C) 68.57 (s, 1 C) 125.48 (s, 2 C) 127.15 (s, 1 C) 129.30 (s, 2 C) 141.31 (s, 1 C) 166.59 (s, 1 C).



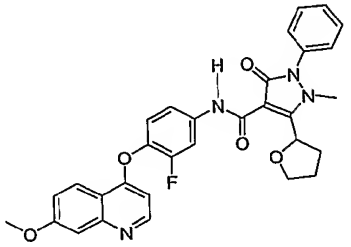
Step 2: Lithium 3-oxo-4-phenylmorpholine-2-carboxylate. A dry 100 mL Schlenk-type flask was fitted with a nitrogen/vacuum line and charged with 2-bromo-1,3,5-tri-tert-

butylbenzene (0.521 g, 1.601 mmol), 20 mL dry THF, and a stirbar. The solution was cooled to -78 °C and treated with 2.5M butyllithium (0.582 ml, 1.456 mmol). The reaction was stirred for 15min and treated with 4-phenylmorpholin-3-one (0.258 g, 1.456 mmol) dissolved in 2 mL dry THF dropwise over 5 min. The reaction was stirred for 2 h at -78 °C. The side arm compartment of the Schlenk-type flask was charged with ~1g dry ice. The system was sealed, and the dry ice was allowed to sublime into the solution. After 30 min, a nitrogen needle was fitted to the flask, and a solid was noted in the solution. The cooling bath was removed, which caused the solids to bubble (presumably dry ice). The solution was allowed to warm to RT overnight. The solution was diluted with 40 mL water and extracted with dichloromethane (2x10 mL). The water was concentrated *in vacuo* and dried at 60 °C and 0.15 mmHg to afford lithium 3-oxo-4-phenylmorpholine-2-carboxylate (0.200 g, 60.5% yield). ^{1}H NMR (400 MHz, D_2O) 3.72 (t, J=5.23 Hz, 2 H), 3.99 (dt, J=12.10, 5.29 Hz, 1 H), 4.08 (dt, J=12.15, 5.22 Hz, 1 H), 4.61 (s, 1 H), 7.24 - 7.28 (m, 2 H), 7.32 (tt, 1 H), 7.38 - 7.44 (m, 2 H).



Step 3: N-(3-Fluoro-4-(7-methoxyquinolin-4-yloxy)phenyl)-3-oxo-4-phenylmorpholine-2-carboxamide. A dry, 10 mL schlenk-type flask was charged with a stirbar, lithium 3-oxo-4-phenylmorpholine-2-carboxylate (0.096 g, 0.42 mmol), triethylammonium hydrochloride (0.058 g, 0.42 mmol), 3*H*-[1,2,3]triazolo[4,5-b]pyridin-3-ol (0.072 g, 0.53 mmol), and evacuated. The flask was back-filled with nitrogen and treated with 2 mL dry THF and 1 mL dry NMP. To the stirring solution was added Si-DCC (0.55 g, 0.53 mmol) followed by3-fluoro-4-(7-methoxyquinolin-4-yloxy)benzenamine (0.100 g, 0.35 mmol). The reaction was stirred for 3 d at RT, and then 60 °C for 24 h. The slurry was filtered through a 0.22 μm frit, and the THF removed. The crude was purified by HPLC (Waters Spherisorb S5 column (PN PSS830195, 20 X 250 mm, 60 Å pore, 5 μm particle size)) to afford the title compound (0.026 g, 15.2% yield) ^{1}H NMR (400 MHz, Chloroform-d) 3.74 (ddd, J=12.32, 3.72, 3.52 Hz, 1 H), 3.95 - 4.03 (m, 4 H), 4.23 (dt, J=12.42, 3.91 Hz, 1 H), 4.27 - 4.38 (m, 1 H), 5.06 (s, 1 H), 6.37 (dd, J=5.23, 1.12 Hz, 1 H), 7.20 (t, J=8.56 Hz, 1 H), 7.24 (dd, J=9.15, 2.49 Hz, 1 H), 7.27 (ddd, J=8.83, 2.47, 1.12 Hz, 1 H), 7.32 - 7.41 (m, 3 H), 7.43 (d, J=2.45 Hz, 1 H), 7.46 - 7.51 (m, 2 H), 7.81 (dd, J=12.03, 2.35 Hz, 1 H), 8.26 (d, J=9.19 Hz, 1 H), 8.59 (d, J=5.18 Hz, 1 H), 9.66 (br. s., 1 H). MS (ESI pos. ion) m/z = 488, calc'd for $C_{27}H_{22}FN_3O_5$ 487.

The following additional compounds can also be made using the methodology generally set forth above: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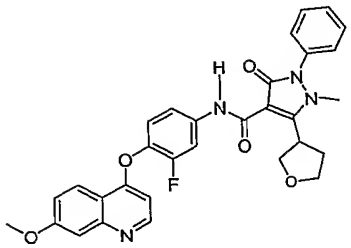
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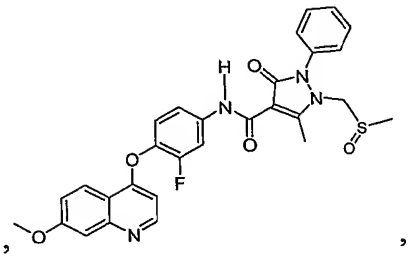
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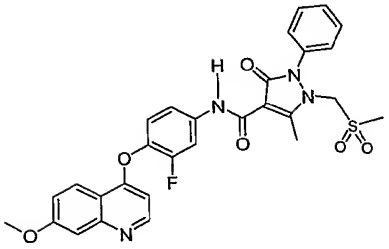
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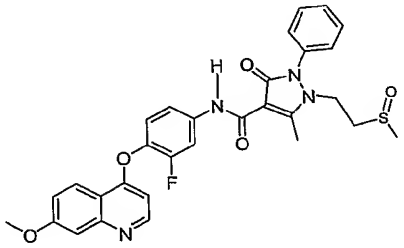
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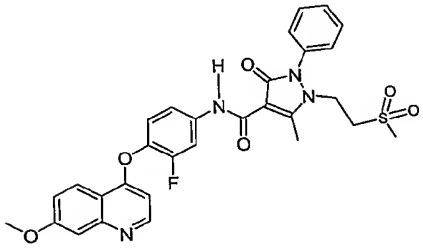
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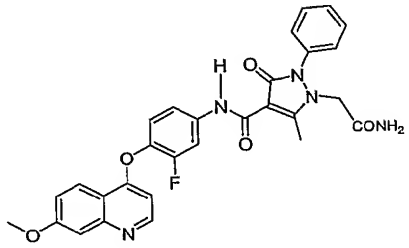
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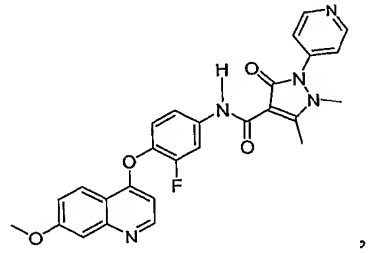
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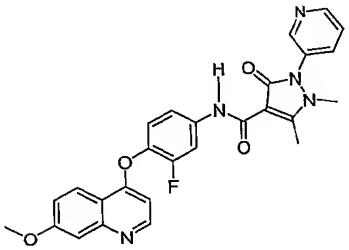
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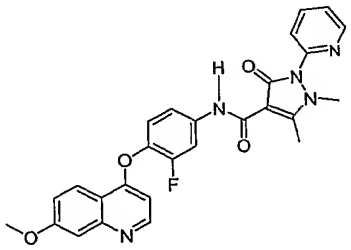
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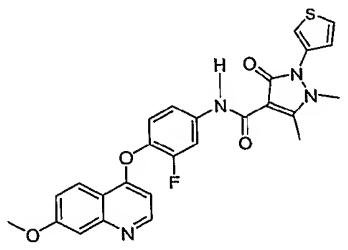
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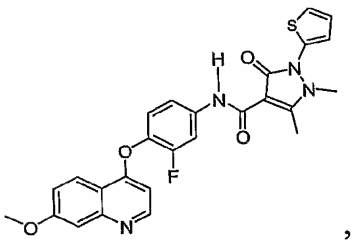
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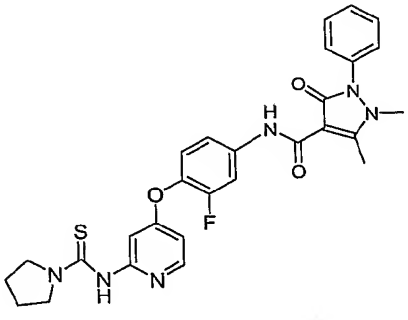
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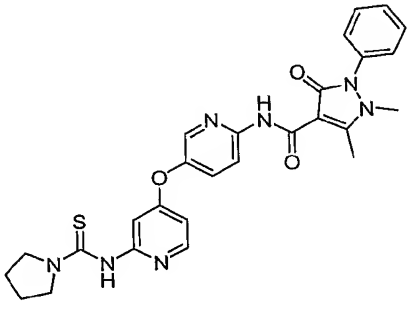
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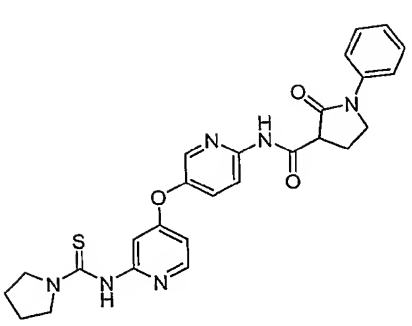
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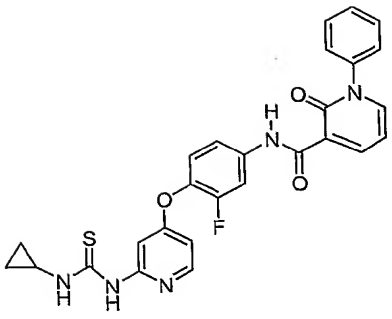
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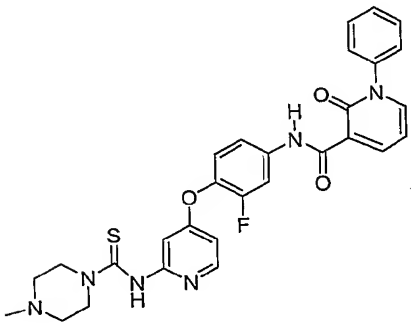
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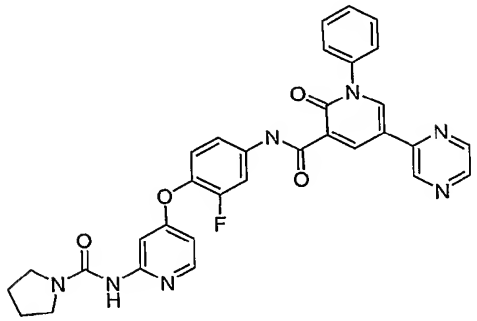
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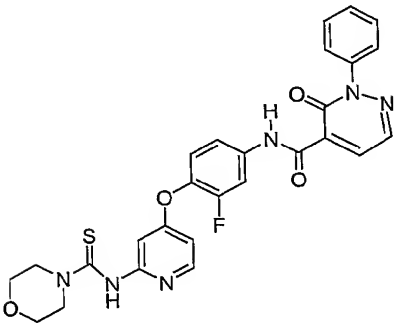
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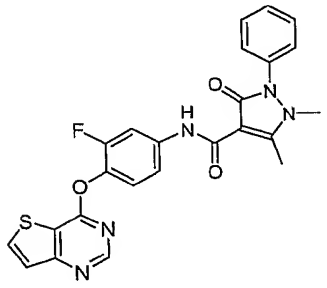
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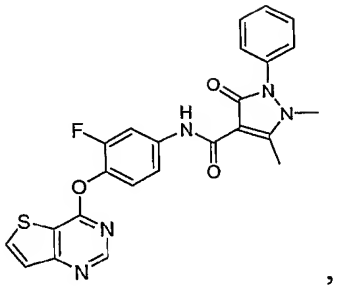
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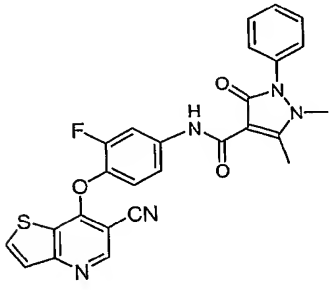
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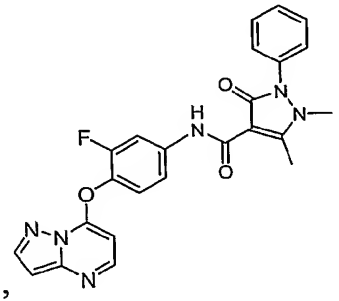
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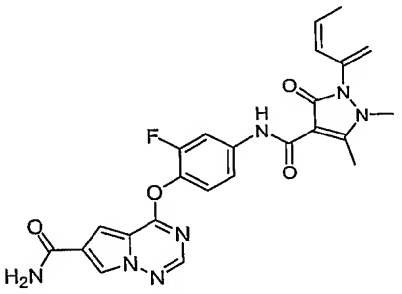
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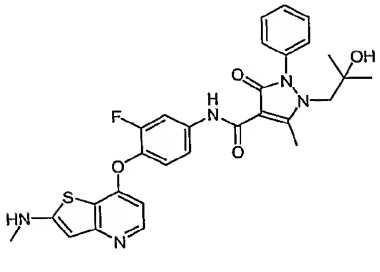
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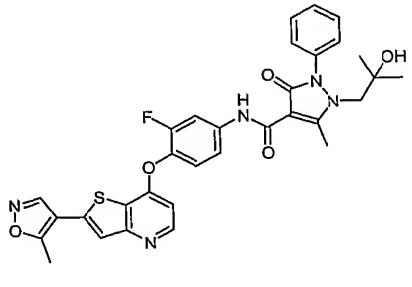
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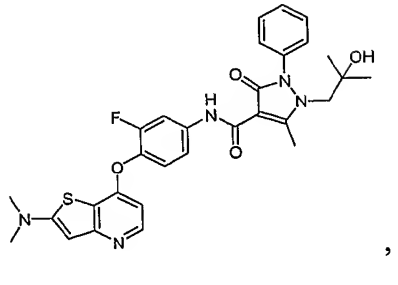
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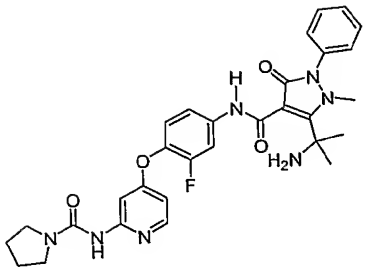
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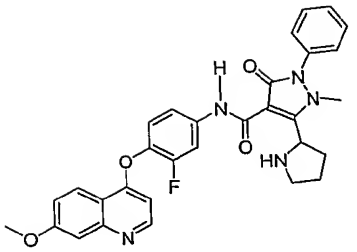
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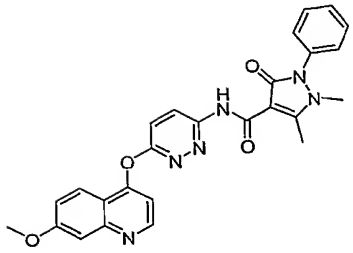
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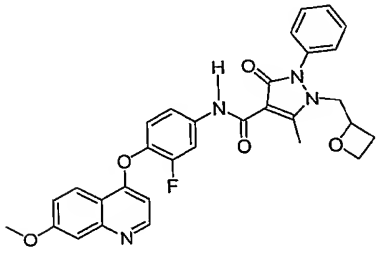
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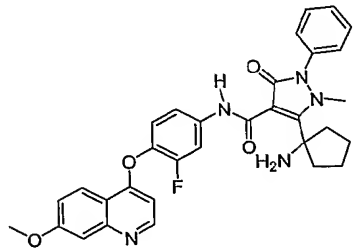
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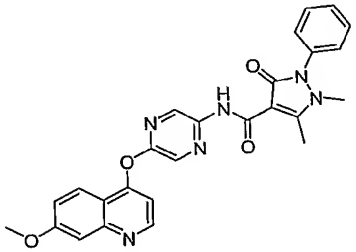
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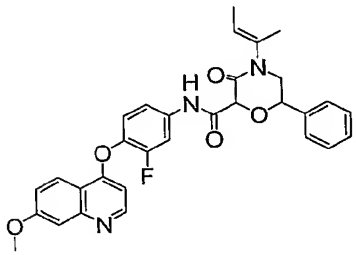
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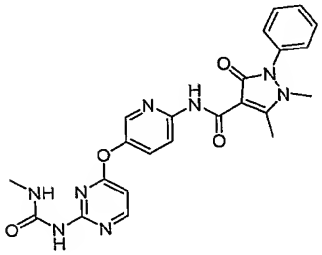
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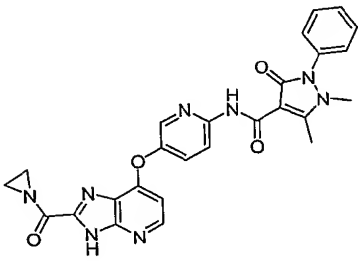
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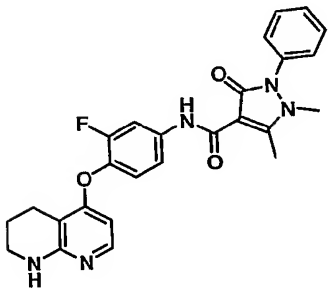
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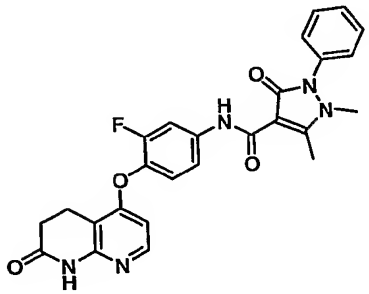
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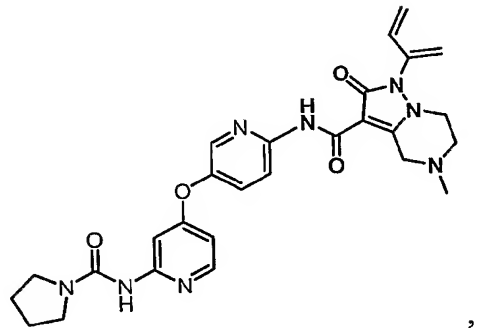
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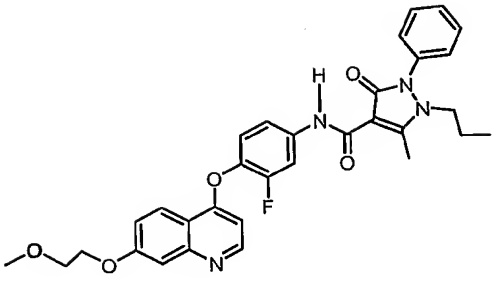
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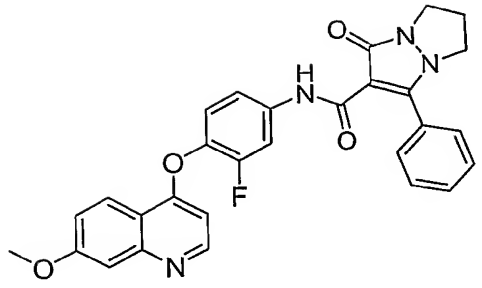
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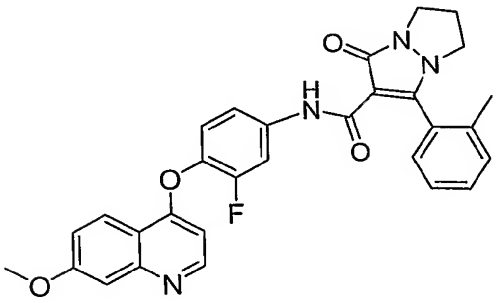
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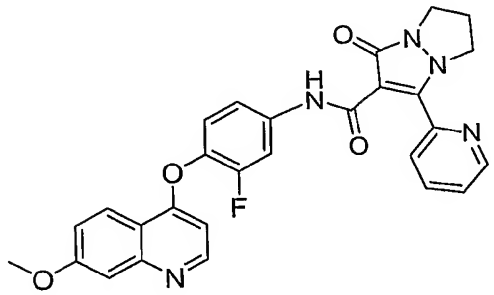
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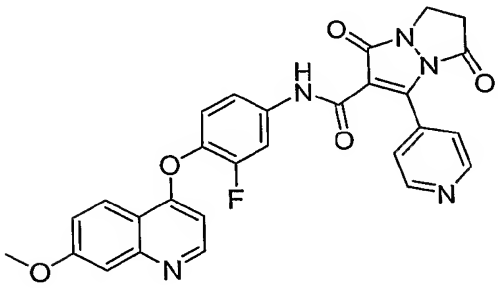
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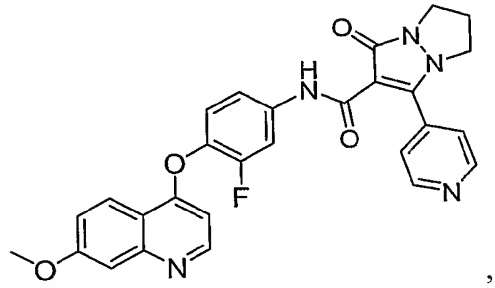
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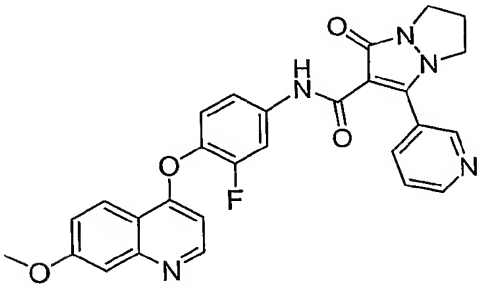


Although the pharmacological properties of the compounds of Formulas I-II vary with structural change, in general, activity possessed by compounds of Formulas I-II may be demonstrated *in vivo*. The pharmacological properties of the compounds of this invention may be confirmed by a number of pharmacological *in vitro* assays. The exemplified pharmacological assays, which follow have been carried out with the compounds according to the invention and their salts. Compounds of the present invention showed inhibition of c-Met kinase at doses less than 2 μM.

BIOLOGICAL TESTING

The efficacy of the compounds of the invention as inhibitors of HGF related activity is demonstrated as follows.

c-Met receptor assay

Cloning, Expression and Purification of c-Met Kinase Domain

A PCR product covering residues 1058-1365 of c-Met (c-Met kinase domain) is generated from Human Liver QuickClone™ cDNA (Invitrogen) using forward primer 5'-ATTGACGGATCCATGCTAAATCCAGAGCTGGTCCAGGCA-3' (SEQ ID NO. 1) and reverse primer 5'-ACAACAGAATTCAATACGGAGCGACACATTTTACGTT-3' (SEQ ID NO. 2). The PCR product is cloned into a modified pFastBac1 expression vector (harboring the gene for *S. japonicum* glutathione S-transferase immediately upstream of the multiple cloning site) using standard molecular biological techniques. The GST-c-Met kinase domain fusion (GST-Met) gene is transposed into full-length baculovirus DNA using the BacToBac™ system (Invitrogen). High5 cells are infected with the recombinant baculovirus for 72 h at 27°C. The infected cells are harvested by centrifugation and the pellet is stored at –80°C. The pellet is resuspended in buffer A (50 mM HEPES, pH 8.0, 0.25 M NaCl, 10 mM 2-mercaptoethanol, 10% (w/v) glycerol, 0.5 % (v/v) protease inhibitor cocktail (Sigma P8340), stirred at 4°C to homogeneity, and the cells are disrupted by microfluidization (Microfluidics) at 10,000 psi. The resulting lysate is centrifuged at 50,000 x *g* for 90 min at 4 °C, and the supernatant is adsorbed onto 10 mL of glutathione sepharose™ 4B (Amersham) by batch method. The slurry is rocked gently overnight at 4°C. The glutathione resin is harvested by centrifugation and washed three times with 40 mL buffer A by batch method. The resin is washed three times with buffer B (buffer A adjusted to 0.1 M NaCl, less protease inhibitors). The protein is eluted with buffer B containing 25 mM reduced glutathione. Eluted fractions are analyzed by SDS-PAGE and concentrated to <10 mL (~10 mg/mL total protein). The concentrated protein is separated by Superdex™ 200 (Amersham) size exclusion

chromatography in buffer C (25 mM Tris, pH 7.5, 0.1 M NaCl, 10 mM 2-mercaptoethanol, 10% glycerol). The fractions are analyzed by SDS-PAGE and the appropriate fractions are pooled and concentrated to ~1 mg/mL. The protein is aliquotted and stored at –80°C.

Alternative purification of human GST-cMET from Baculovirus cells

Baculovirus cells are broken in 5x (volume/weight) of Lysis Buffer (50 mM HEPES, pH 8.0, 0.25 M NaCl, 5 mM mercaptoethanol, 10% glycerol plus Complete Protease Inhibitors (Roche (#10019600), 1 tablet per 50 mL buffer). The lysed cell suspension is centrifuged at 100,000 x g (29,300 rpm) in a Beckman ultracentrifuge Ti45 rotor for 1 h. The supernatant is incubated with 10 ml of Glutathione Sepharose 4B from Amersham Biosciences (#27-4574-01). Incubation is carried out overnight in a cold room (approximately 8°C). The resin and supernatant is poured into an appropriately sized disposable column and the flow through supernatant was collected. The resin is washed with 10 column volumes (100 mL) of Lysis Buffer. The GST-cMET is eluted with 45 mL of 10 mM Glutathione (Sigma #G-4251) in Lysis Buffer. The elution is collected as 15 mL fractions. Aliquots of the elution fractions are run on SDS PAGE (12% Tris Glycine gel, Invitrogen, #EC6005BOX). The gel is stained with 0.25% Coomassie Blue stain. Fractions with GST-cMET are concentrated with a Vivaspin 20 mL Concentrator (#VS2002; 10,00 MW cutoff) to a final volume less than 2.0 ml. The concentrated GST-cMET solution is applied to a Superdex 75 16/60 column (Amersham Biosciences #17-1068-01) equilibrated with 25 mM Tris, pH 7.5, 100 mM NaCl, 10 mM mercaptoethanol, 10% glycerol. The GST-cMET is eluted with an isocratic run of the above buffer, with the eluent collected in 1.0 mL fractions. Fractions with significant OD_{280} readings are run on another 12% Tris Glycine gel. The peak tubes with GST-cMET are pooled and the OD_{280} is read with the column buffer listed above as the blank buffer.

Phosphorylation of the purified GST-cMET is performed by incubating the protein for 3 h at RT with the following:

	Final concentration
a) 100 mM ATP (Sigma #A7699)	25 mM
b) 1.0 M $MgCl_2$ (Sigma #M-0250)	100 mM
c) 200 mM Sodium Orthovanadate (Sigma #S-6508)	15 mM
d) 1.0 M Tris-HCl, pH 7.00 (in house)	50 mM
e) H_20	
f) GST-cMET	0.2 - 0.5 mg/mL

After incubation, the solution is concentrated in a Vivaspin 20 ml Concentrator to a volume less than 2.00 ml. The solution is applied to the same Superdex 75 16/60 column used above after re-equilibration. The GST-cMET is eluted as described above. The elution fractions corresponding to the first eluted peak on the chromatogram are run on a 12% Tris Glycine gel, as above, to identify the fractions with GST-cMET. Fractions are pooled and the OD_{280} is read with the column buffer used as the blank.

A Kinase reaction Buffer is prepared as follows:

			Per 1 L
60 mM HEPES pH 7.4	1 M stock	16.7 X	60 mL
50 mM NaCl	5 M stock	100 X	10 mL
20 mM $MgCl_2$	1 M stock	50 X	20 mL
5 mM $MnCl_2$	1 M stock	200 X	5 mL

When the assay is carried out, freshly add:

2 mM DTT	1 M stock	500 X
0.05 % BSA	5 % stock	100 X
0.1 mM Na_3OV_4	0.1 M stock	1000 X

The HTRF buffer contains:
50 mM Tris-HCl (pH 7.5), 100 mM NaCl, 0.1 % BSA, 0.05 % Tween 20,5mM EDTA

Fresh add SA-APC (PJ25S Phycolink Streptavidin-Allophycocyanin Conjugate, Prozyme Inc.) and Eu-PT66 (Eu-W1024 labeled anti-phosphorotyrosine antibody PT66, AD0069, Lot 168465, Perkin-Elmer Inc.) to reach the final concentration:

0.1 nM final Eu-PT66
11 nM final SA-APC

Methods:

1. Dilute GST-cMet (P) enzyme in kinase buffer as follows:
Prepare 8 nM GST-cMet (P) working solution (7.32 μM to 8 nM, 915 X, 10 μL to 9.15 mL). In a 96 well clear plate [Costar # 3365] add 100 μL in eleven columns, in one column add 100 μL kinase reaction buffer alone.

2. Assay plate preparation:

Use Biomek FX to transfer 10 μL 8 nM GST-cMet (P) enzyme, 48.4 μL kinase reaction buffer, 1.6 μL compound (in DMSO) (Start concentration at 10 mM, 1 mM and 0.1 mM, sequential dilution 1:3 to reach 10 test points) in a 96 well costar clear plate [Costar # 3365], mix several times. Then incubate the plate at RT for 30 min.

3. Prepare Gastrin and ATP working solution in kinase reaction buffer as follows:

Prepare 4 μM Gastrin and 16 μM ATP working solution

		Per 10 mL
Gastrin 4 μM stock	(500 μM to 4 μM, 125 X)	80 μL
ATP 16 μM stock	(1000 μM to 16 μM, 62.5 X)	160 μL

Use Biomek FX to add 20 μl ATP and Gastrin working solution to the assay plate to start reaction, incubate the plate at RT for 1 h.

4. Transfer 5 μL reaction product at the end of 1 h into 80 μL HTRF buffer in black plate [Costar # 3356], read on Discover after 30 min incubation.

Assay condition summary:

K_M ATP *	-	6 μM
[ATP]	-	4 μM
K_M Gastrin/p(EY)	-	3.8 μM
[gastrin]	-	1 μM
[enzyme]	-	1 nM

K_M ATP, K_M gastrin for various enzymes were determined by HTRF/^{33}P labeling and HTRF methods.

Examples 1-28, 30, 33-34, 36-37, and 39-48 exhibited activity with IC_{50} values less than 0.5 μM.

c-Met cell-based autophosphorylation assay

Human PC3 and mouse CT26 cells are available obtained from ATCC. The cells were cultured in a growth medium containing RPMI 1640, penicillin/streptomycin/glutamine (1X) and 5% FBS. 2 x 10^4 cells in medium were plated per well in a 96 well plate and incubated at 37 °C overnight. The cells were serum-starved by replacing the growth media with basic medium (DMEM low glucose + 0.1 BSA, 120 μL per well) at 37 °C for 16 h. Compounds

(either 1 mM and 0.2 mM) in 100% DMSO were serially diluted (1:3) 3333 fold on a 96 well plate, diluting 1:3 with DMSO from column 1 to 11 (columns 6 and 12 receive no compound). Compound samples (2.4 μL per well) were diluted with basic medium (240 μL) in a 96 well plate. The cells were washed once with basic medium (GIBCO, DMEM 11885-076) then compound solution was added (100 μL). The cells were incubated at 37 °C for 1 h. A (2 mg/mL) solution of CHO-HGF (7.5 μL) was diluted with 30 mL basic medium to provide a final concentration of 500 ng/mL. This HGF-containing media (120 μL) was transferred to a 96 well plate. Compounds (1.2 μL) was added to the HGF-containing media and mixed well. The mixture of media/HGF/compound (100 μL) was added to the cells (final HGF concentration - 250 ng/mL) then incubated at 37 °C for 10 min. A cell lysate buffer (20 mL) was prepared containing 1% Triton X-100, 50 mM Tris pH 8.0, 100 mM NaCl, Protease inhibitor (Sigma, #P-8340) 200 μL, Roche Protease inhibitor (Complete, # 1-697-498) 2 tablets, Phosphatase Inhibitor II (Sigma, #P-5726) 200 μL, and a sodium vanadate solution (containing 900 μL PBS, 100 μL 300 mM $NaVO_3$, 6 μL H_2O_2 (30% stock) and stirred at RT for 15 min) (90 μL). The cells were washed once with ice cold 1X PBS (GIBCO, #14190-136), then lysis buffer (60 μL) was added and the cells were incubated on ice for 20 min.

The IGEN assay was performed as follows: Dynabeads M-280 streptavidin beads were pre-incubated with biotinylated anti-human HGFR (240 μL anti-human-HGFR (R&D system, BAF527 or BAF328) @ 100 μg/mL + 360 μL Beads (IGEN #10029 + 5.4 μL buffer – PBS/1% BSA/0.1% Tween20) by rotating for 30 min at RT. Antibody beads (25 μL) were transferred to a 96 well plate. Cell lysate solution (25 μL) was transferred added and the plate was shaken at RT for 1 h. Anti-phosphotyrosine 4G10 (Upstate 05-321) (19.7 μL antibody + 6 mL 1X PBS) (12.5 μL) was added to each well, then incubated for 1 h at RT. Anti-mouse IgG ORI-Tag (ORIGEN #110087) (24 μL Antibody + 6 mL buffer) (12.5 μL) was added to each well, then incubated at RT for 30 min. 1X PBS (175 μL) was added to each well and the electrochemiluminescence was read by an IGEN M8. Raw data was analyzed using a 4-parameter fit equation in XLFit. IC_{50} values are then determined using Grafit software. Examples 2, 4, 6-8, 11, 13, 15-21, 23-26, 36-37, 39, 41, and 43-44 exhibited activity in PC3 cells with IC_{50} values less than 1.0 μM. Examples 2, 4, 6-8, 11-13, 15-21, 23-26, 36-37, 41, and 43-44 exhibited activity in CT26 cells with IC_{50} values less than 1.0 μM.

HUVEC Proliferation Assay

Human Umbilical Vein Endothelial cells are purchased from Clonetics, Inc., as cryopreserved cells harvested from a pool of donors. These cells, at passage 1, are thawed and expanded in EBM-2 complete medium, until passage 2 or 3. The cells are trypsinized, washed in DMEM + 10% FBS + antibiotics, and spun at 1000 rpm for 10 min. Prior to centrifugation of the cells, a small amount is collected for a cell count. After centrifugation, the medium is discarded, and the cells are resuspended in the appropriate volume of DMEM + 10% FBS + antibiotics to achieve a concentration of 3×10^5 cells/mL. Another cell count is performed to confirm the cell concentration. The cells are diluted to 3×10^4 cells/mL in DMEM + 10% FBS + antibiotics, and 100 µL of cells are added to a 96-well plate. The cells are incubated at 37 °C for 22 h.

Prior to the completion of the incubation period, compound dilutions are prepared. Five-point, five-fold serial dilutions are prepared in DMSO, at concentrations 400-fold greater than the final concentrations desired. 2.5 µL of each compound dilution are diluted further in a total of 1 mL DMEM + 10% FBS + antibiotics (400x dilution). Medium containing 0.25% DMSO is also prepared for the 0 µM compound sample. At the 22 h timepoint, the medium is removed from the cells, and 100 µL of each compound dilution is added. The cells are incubated at 37 °C for 2-3 h.

During the compound pre-incubation period, the growth factors are diluted to the appropriate concentrations. Solutions of DMEM + 10% FBS + antibiotics, containing either VEGF or bFGF at the following concentrations: 50, 10, 2, 0.4, 0.08, and 0 ng/mL are prepared. For the compound-treated cells, solutions of VEGF at 550 ng/mL or bFGF at 220 ng/mL for 50 ng/mL or 20 ng/mL final concentrations, respectively, are prepared since 10 µL of each will be added to the cells (110 µL final volume). At the appropriate time after adding the compounds, the growth factors are added. VEGF is added to one set of plates, while bFGF is added to another set of plates. For the growth factor control curves, the media on wells B4-G6 of plates 1 and 2 are replaced with media containing VEGF or bFGF at the varying concentrations (50–0 ng/mL). The cells are incubated at 37 °C for an additional 72 h.

At the completion of the 72 h incubation period, the medium is removed, and the cells are washed twice with PBS. After the second wash with PBS, the plates are tapped gently to remove excess PBS, and the cells are placed at –70 °C for at least 30 min. The cells are thawed and analyzed using the CyQuant fluorescent dye (Molecular Probes C-7026), following the manufacturer's recommendations. The plates are read on a Victor/Wallac 1420

workstation at 485 nm/530 nm (excitation/emission). Raw data are collected and analyzed using a 4-parameter fit equation in XLFit. IC_{50} values are then determined.

Rat Corneal Neovascularization Micropocket Model

In Life Aspects: Female Sprague Dawley rats weighing approximately 250 g were randomized into one of five treatment groups. Pretreatment with the vehicle or compound was administered orally, 24 h prior to surgery and continued once a day for seven additional days. On the day of surgery, the rats were temporarily anesthetized in an Isofluorane gas chamber (delivering 2.5 L/min oxygen + 5% Isofluorane). An othoscope was then placed inside the mouth of the animal to visualize the vocal cords. A tip-blunted wire was advanced in between the vocal cords and used as a guide for the placement of an endotracheal Teflon tube (Small Parts Inc. TFE-standard Wall R-SWTT-18). A volume-controlled ventilator (Harvard Apparatus, Inc. Model 683) was connected to the endotracheal tube to deliver a mixture of oxygen and 3% Isofluorane. Upon achieving deep anesthesia, the whiskers were cut short and the eye areas and eyes gently washed with Betadine soap and rinsed with sterile saline. The corneas were irrigated with one to two drops of Proparacaine HCl ophthalmic topical anesthetic solution (0.5%) (Bausch and Lomb Pharmaceuticals, Tampa FL). The rat was then positioned under the dissecting microscope and the corneal surface brought into focus. A vertical incision was made on the midline of the cornea using a diamond blade knife. A pocket was created by using fine scissors to separate the connective tissue layers of the stroma, tunneling towards the limbus of the eye. The distance between the apex of the pocket and the limbus was approximately 1.5 mm. After the pocket had been made, the soaked nitrocellulose disk filter (Gelman Sciences, Ann Arbor MI.) was inserted under the lip of the pocket. This surgical procedure was performed on both eyes. rHu-bFGF soaked disks were placed into the right eye, and the rHu-VEGF soaked disks were placed into the left eye. Vehicle soaked disks were placed in both eyes. The disk was pushed into position at the desired distance from the limbal vessels. Ophthalmic antibiotic ointment was applied to the eye to prevent drying and infection. After seven days, the rats were euthanized by CO_2 asphyxiation, and the eyes enucleated. The retinal hemisphere of the eye was windowed to facilitate fixation, and the eye placed into formalin overnight.

Post Mortem Aspects: After 24 h in fixative, the corneal region of interest was dissected out from the eye, using fine forceps and a razorblade. The retinal hemisphere was trimmed off and the lens extracted and discarded. The corneal dome was bisected and the superfluous cornea trimmed off. The iris, conjunctiva and associated limbal glands were then

carefully teased away. Final cuts were made to generate a square 3 x 3 mm containing the disk, the limbus, and the entire zone of neovascularization.

Gross Image Recording: The corneal specimens were digitally photographed using a Sony CatsEye DKC5000 camera (A.G. Heinz, Irvine CA) mounted on a Nikon SMZ-U stereo microscope (A.G. Heinz). The corneas were submerged in distilled water and photographed via trans-illumination at approximately 5.0 diameters magnification.

Image analysis: Numerical endpoints were generated using digital micrographs collected from the whole mount corneas after trimming and were used for image analysis on the Metamorph image analysis system (Universal Imaging Corporation, West Chester PA). Three measurements were taken: Disk placement distance from the limbus, number of vessels intersecting a 2.0 mm perpendicular line at the midpoint of the disk placement distance, and percent blood vessel area of the diffusion determined by thresholding.

General Formulations:

0.1% BSA in PBS vehicle: 0.025 g of BSA was added to 25.0 mL of sterile 1X phosphate buffered saline, gently shaken until fully dissolved, and filtered at 0.2 μM. Individual 1.0 mL samples were aliquoted into 25 single-use vials, and stored at –20 °C until use. For the rHu-bFGF disks, a vial of this 0.1% BSA solution was allowed to thaw at room temperature. Once thawed, 10 μL of a 100 mM stock solution of DTT was added to the 1 ml BSA vial to yield a final concentration of 1 mM DTT in 0.1% BSA.

rHu-VEGF Dilutions: Prior to the disk implant surgery, 23.8 μL of the 0.1% BSA vehicle above was added to a 10 μg rHu-VEGF lyophilized vial yielding a final concentration of 10 μM.

rHu-bFGF: Stock concentration of 180 ng/μL: R&D rHu- bFGF: Added 139 μL of the appropriate vehicle above to the 25 μg vial lyophilized vial. 13.3 μL of the [180 ng/μL] stock vial and added 26.6 μL of vehicle to yield a final concentration of 3.75 μM concentration.

Nitro-cellulose disk preparation: The tip of a 20-gauge needle was cut off square and beveled with emery paper to create a punch. This tip was then used to cut out ≅ 0.5 mm diameter disks from a nitrocellulose filter paper sheet (Gelman Sciences). Prepared disks were then placed into Eppendorf microfuge tubes containing solutions of either 0.1% BSA in PBS vehicle, 10 μM rHu-VEGF (R&D Systems, Minneapolis, MN), or 3.75 μM rHu-bFGF (R&D Systems, Minneapolis, MN) and allowed to soak for 45-60 min before use. Each nitrocellulose filter disk absorbs approximately 0.1 μL of solution.

In the rat micropocket assay, compounds of the present invention will inhibit angiogenesis at a dose of less than 50 mg/kg/day.

Tumor model

A431 cells (ATCC) are expanded in culture, harvested and injected subcutaneously into 5-8 week old female nude mice (CD1 nu/nu, Charles River Labs) (n = 5-15). Subsequent administration of compound by oral gavage (10 - 200 mpk/dose) begins anywhere from day 0 to day 29 post tumor cell challenge and generally continues either once or twice a day for the duration of the experiment. Progression of tumor growth is followed by three dimensional caliper measurements and recorded as a function of time. Initial statistical analysis is done by repeated measures analysis of variance (RMANOVA), followed by Scheffe post hoc testing for multiple comparisons. Vehicle alone (Ora-Plus, pH 2.0) is the negative control. Compounds of the present invention will be active at doses less than 150 mpk.

Tumor models

Human glioma tumor cells (U87MG cells, ATCC) are expanded in culture, harvested and injected subcutaneously into 5-8 week old female nude mice (CD1 nu/nu, Charles River Labs) (n=10). Subsequent administration of compound by oral gavage or by IP (10-100 mpk/dose) begins anywhere from day 0 to day 29 post tumor cell challenge and generally continues either once or twice a day for the duration of the experiment. Progression of tumor growth is followed by three dimensional caliper measurements and recorded as a function of time. Initial statistical analysis is done by repeated measures analysis of variance (RMANOVA), followed by Scheffe post hoc testing for multiple comparisons. Vehicle alone (captisol, or the like) is the negative control. Compounds of the present invention will be active at 150 mpk.

Human gastric adenocarcinoma tumor cells (MKN45 cells, ATCC) are expanded in culture, harvested and injected subcutaneously into 5-8 week old female nude mice (CD1 nu/nu, Charles River Labs) (n=10). Subsequent administration of compound by oral gavage or by IP (10-100 mpk/dose) begins anywhere from day 0 to day 29 post tumor cell challenge and generally continues either once or twice a day for the duration of the experiment. Progression of tumor growth is followed by three dimensional caliper measurements and recorded as a function of time. Initial statistical analysis is done by repeated measures analysis of variance (RMANOVA), followed by Scheffe post hoc testing for multiple comparisons. Vehicle alone (captisol, or the like) is the negative control. Compounds of the present invention will be active at 150 mpk.

FORMULATIONS

Also embraced within this invention is a class of pharmaceutical compositions comprising the active compounds of Formula I-II in association with one or more non-toxic, pharmaceutically-acceptable carriers and/or diluents and/or adjuvants (collectively referred to

herein as "carrier" materials) and, if desired, other active ingredients. The active compounds of the present invention may be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. The compounds and compositions of the present invention may, for example, be administered orally, mucosally, topically, rectally, pulmonarily such as by inhalation spray, or parentally including intravascularly, intravenously, intraperitoneally, subcutaneously, intramuscularly intrasternally and infusion techniques, in dosage unit formulations containing conventional pharmaceutically acceptable carriers, adjuvants, and vehicles.

The pharmaceutically active compounds of this invention can be processed in accordance with conventional methods of pharmacy to produce medicinal agents for administration to patients, including humans and other mammals.

For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient. Examples of such dosage units are tablets or capsules. For example, these may contain an amount of active ingredient from about 1 to 2000 mg, preferably from about 1 to 500 mg. A suitable daily dose for a human or other mammal may vary widely depending on the condition of the patient and other factors, but, once again, can be determined using routine methods.

The amount of compounds which are administered and the dosage regimen for treating a disease condition with the compounds and/or compositions of this invention depends on a variety of factors, including the age, weight, sex and medical condition of the subject, the type of disease, the severity of the disease, the route and frequency of administration, and the particular compound employed. Thus, the dosage regimen may vary widely, but can be determined routinely using standard methods. A daily dose of about 0.01 to 500 mg/kg, preferably between about 0.01 and about 50 mg/kg, and more preferably about 0.01 and about 30 mg/kg body weight may be appropriate. The daily dose can be administered in one to four doses per day.

For therapeutic purposes, the active compounds of this invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered per os, the compounds may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanoic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets may contain a controlled-

release formulation as may be provided in a dispersion of active compound in hydroxypropylmethyl cellulose.

In the case of psoriasis and other skin conditions, it may be preferable to apply a topical preparation of compounds of this invention to the affected area two to four times a day.

Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin (*e.g.*, liniments, lotions, ointments, creams, or pastes) and drops suitable for administration to the eye, ear, or nose. A suitable topical dose of active ingredient of a compound of the invention is 0.1 mg to 150 mg administered one to four, preferably one or two times daily. For topical administration, the active ingredient may comprise from 0.001% to 10% w/w, *e.g.*, from 1% to 2% by weight of the formulation, although it may comprise as much as 10% w/w, but preferably not more than 5% w/w, and more preferably from 0.1% to 1% of the formulation.

When formulated in an ointment, the active ingredients may be employed with either paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base. If desired, the aqueous phase of the cream base may include, for example at least 30% w/w of a polyhydric alcohol such as propylene glycol, butane-1,3-diol, mannitol, sorbitol, glycerol, polyethylene glycol and mixtures thereof. The topical formulation may desirably include a compound, which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include DMSO and related analogs.

The compounds of this invention can also be administered by a transdermal device. Preferably transdermal administration will be accomplished using a patch either of the reservoir and porous membrane type or of a solid matrix variety. In either case, the active agent is delivered continuously from the reservoir or microcapsules through a membrane into the active agent permeable adhesive, which is in contact with the skin or mucosa of the recipient. If the active agent is absorbed through the skin, a controlled and predetermined flow of the active agent is administered to the recipient. In the case of microcapsules, the encapsulating agent may also function as the membrane.

The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier, it may comprise a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier, which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make-up the so-called emulsifying wax, and the wax

together with the oil and fat make up the so-called emulsifying ointment base, which forms the oily dispersed phase of the cream formulations. Emulsifiers and emulsion stabilizers suitable for use in the formulation of the present invention include Tween 60, Span 80, cetostearyl alcohol, myristyl alcohol, glyceryl monostearate, sodium lauryl sulfate, glyceryl distearate alone or with a wax, or other materials well known in the art.

The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties, since the solubility of the active compound in most oils likely to be used in pharmaceutical emulsion formulations is very low. Thus, the cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters may be used. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils can be used.

Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredients are dissolved or suspended in suitable carrier, especially an aqueous solvent for the active ingredients. The active ingredients are preferably present in such formulations in a concentration of 0.5 to 20%, advantageously 0.5 to 10% and particularly about 1.5% w/w.

Formulations for parenteral administration may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules using one or more of the carriers or diluents mentioned for use in the formulations for oral administration or by using other suitable dispersing or wetting agents and suspending agents. The compounds may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, tragacanth gum, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art. The active ingredient may also be administered by injection as a composition with suitable carriers including saline, dextrose, or water, or with cyclodextrin (ie. Captisol), cosolvent solubilization (ie. propylene glycol) or micellar solubilization (ie. Tween 80).

The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water,

Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed, including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

For pulmonary administration, the pharmaceutical composition may be administered in the form of an aerosol or with an inhaler including dry powder aerosol.

Suppositories for rectal administration of the drug can be prepared by mixing the drug with a suitable non-irritating excipient such as cocoa butter and polyethylene glycols that are solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum and release the drug.

The pharmaceutical compositions may be subjected to conventional pharmaceutical operations such as sterilization and/or may contain conventional adjuvants, such as preservatives, stabilizers, wetting agents, emulsifiers, buffers etc. Tablets and pills can additionally be prepared with enteric coatings. Such compositions may also comprise adjuvants, such as wetting, sweetening, flavoring, and perfuming agents.

The foregoing is merely illustrative of the invention and is not intended to limit the invention to the disclosed compounds. Variations and changes, which are obvious to one skilled in the art are intended to be within the scope and nature of the invention, which are defined, in the appended claims.

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

No unacceptable toxological effects are expected when compounds of the present invention are administered in accordance with the present invention.

All mentioned references, patents, applications and publications, are hereby incorporated by reference in their entirety, as if here written.

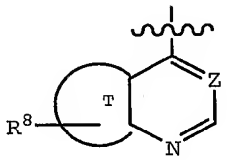
WHAT IS CLAIMED IS:

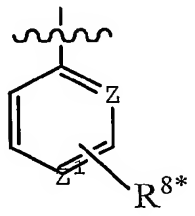
1. A compound of formula I

R-X-W-Y-R^1 **I**

enantiomers, diastereomers, salts solvates, and N-oxides thereof wherein

R is





; or

T is selected from phenyl, 5-6-membered heteroaryl, or 5-6 membered heterocyclyl;

Z is selected from N or CR^7;

Z^1 is selected from N or CR^7;

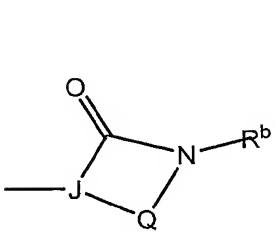
W is an substituted or unsubstituted phenyl, a substituted or unsubstituted benzomorpholinyl, a substituted or unsubstituted 6-membered nitrogen containing heteroaryl; a substituted or unsubstituted c_{3-7}cycloalkyl, c_{1-6}alky and c_{1-6}alkynyl;

X is selected from O, S, S(=O), SO_2, NR^2 and CR^3R^4;

Y is selected from $-NR^aC(=O)-(CR^3R^4)_p-$, $-NR^aC(=S)-(CR^3R^4)_p-$, $-NR^a-(CR^3R^4)_p-$, $-NR^a-(CR^3R^4)_pC(=O)-$, $-NR^a-(CR^3R^4)_pC(=S)-$, $-NR^aS(=O)_t-$, $-NR^aS(=O)_t-(CR^3R^4)_p-$, $-C(=O)NR^a-(CR^3R^4)_p-$, and $-NR^a-(CR^3R^4)_p-S(=O)_t-$, and where W is benzomorpholinyl Y may further include -C(=O);

R^a is selected from H, alkyl, heterocyclyl, aryl, arylalkyl, heterocyclylalkyl, cycloalkyl, cycloalkylalkyl, alkenyl and alkynyl; wherein R^a is optionally substituted;

R^1 is a partially unsaturated or saturated ring selected from



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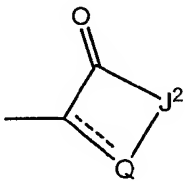

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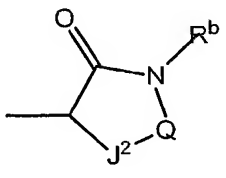

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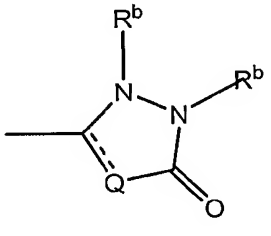
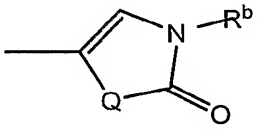


, and



wherein J is N or CR^{4a};

J^2 is O or $CR^{4a}R^{4a}$;

Q is a 1-5 membered saturated or partially unsaturated alkly chain, or a 2-5 membered saturated or partially unsaturated heteroalkyl chain;

R^1 is optionally fused with an optionally substituted phenyl or an optionally substituted 5-6 membered heterocyclyl ring;

wherein R^1 is optionally substituted with one or more substituents independently selected from H, halo, hydroxyl, $R^{5a}R^aN$-, $R^{5a}R^aN$-C_{1-6} alkyl, $R^5(S=O)$-C_{1-6} alky, NR^5R^{5a}-(C=O)-C_{1-6} alky, optionally substituted alkyl, alkenyl hydroxyalkyl, C_{1-6} alkoxy-C_{1-6} alkyl, alkenylalkyl, C_{1-6} alkylthio-C_{1-3} alkyl, -C_{1-6} alkyl-NR^a-C(=O)-OR^5, '-C_{1-3} alkyl-NR^a-(C=O)-R^5, -C_{1-3} alkyl-C(=O)- C_{1-3} alkyl, aminoalkyl, hydroxy-substituted aminoalkyl, hydroxy-substituted haloalkyl, (heterocyclo)hydroxyalkyl, haloC_{1-6}-alkyl, azidoalkyl, optionally substituted aryl-C_{1-6} alkyl, optionally substituted 5-6-membered heterocyclyl-C_{1-6} alkyl, optionally substituted C_{1-6}-alkyl, optionally substituted C_{3-7} cycloalkyl, optionally substituted 5-6 membered heterocyclyl, optionally substituted 5-10 membered heteroaryl, optionally, optionaolly substituted C_{3-6} cycloalkyl, substituted heteroarylalkyl, optionally substituted arylalkyl, and optionally substituted C_{6-10} aryl;

R^2 is selected from H, alkyl, haloalkyl, aryl, heterocyclyl, arylalkyl, heterocyclylalkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl and R^5-carbonyl;

R^3 and R^4 are each independently selected from H, alkyl, aryl, heterocyclyl, arylalkyl, heterocyclylalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, R^6 and alkyl substituted with R^6; alternatively R^3 and R^4, together with the carbon atom they are attached to, form an optionally substituted 3-6 membered ring;

R^{3a} is absent or is selected from H, alkyl, aryl, heterocyclyl, arylalkyl, heterocyclylalkyl, cycloalkyl, cycloalkylalkyl, R^6 and alkyl substituted with R^6;

R^{4a} is absent or is selected from H, halo, -OR^5 –NR^aR^5, alkyl, aryl, heterocyclyl, arylalkyl, heterocyclylalkyl, cycloalkyl, cycloalkylalkyl, R^6 and alkyl substituted with R^6;

R^5 is independently selected at each occurrence from H, alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, alkylaminoalkyl, alkylthioalkyl, arylalkyl, heterocyclylalkyl, cycloalkylalkyl, aryl, heterocyclyl, alkenyl, alkynyl and cycloalkyl;

R^{5a} is independently selected at each occurrence from H, alkyl, haloalkyl, arylalkyl aminoalkyl, heterocyclylalkyl, cycloalkylalkyl, aryl, heterocyclyl, alkenyl, alkynyl and cycloalkyl;

or when R^5 and R^a, or $R^{5a}$and R^a are bonded to the same nitrogen atom, R^a and R^5, or R^a and R^{5a} may independently optionally combine to form a heterocyclo ring.

R^6 is selected from cyano, $-OR^2$, $-SR^2$, halo, $-SO_2R^2$, $-C(=O)R^2$, $-SO_2NR^2R^5$, $-NR^5C(=O)OR^2$, $-NR^5C(=O)NR^5R^2$, $-NR^5C(=O)R^2$, $-CO_2R^2$, $-C(=O)NR^2R^5$ and $-NR^2R^5$;

R^7 is selected from H, halo, cyano, $-C(=O)NR^aR^5$ and alkyl;

R^8 is one or more substituents independently selected at each occurrence from H, cyano, hydroxyl, halo, optionally substituted heterocyclyl, $-C(=O)NR^aR^5$, $-OC(=O)NR^aR^5$, $-NR^aC(=O)OR^5$, $-NR^aC(=O)-R^5$, $R^5R^aN-O_2S-$, R^5O_2S-, $R^5O_2SR^aN-$, R^5R^aN-, alkyl, aminoalkyl, alkylaminoalkyl, alkoxyalkyl, phenylalkyl, heterocyclylalkyl, alkoxy, haloalkoxy, alkylaminoalkoxy, arylalkoxy, heterocyclylalkoxy, cycloalkylalkoxy, heterocyclyl(hydroxyalkoxy), cycloalkyl(hydroxyalkoxy), aryl(hydroxyalkoxy), alkoxyalkoxy, aryloxyalkoxy, heterocyclyloxyalkoxy, cycloalkyloxyalkoxy, aryloxy, heterocyclyloxy, cycloalkyloxy; aryl and heteroaryl, alternatively where R^8 comprises an NR^aR^5 moiety R^a and R^5, together with the nitrogen atom they are attached to, may optionally form a substituted or unsubstituted 4-6 membered ring;

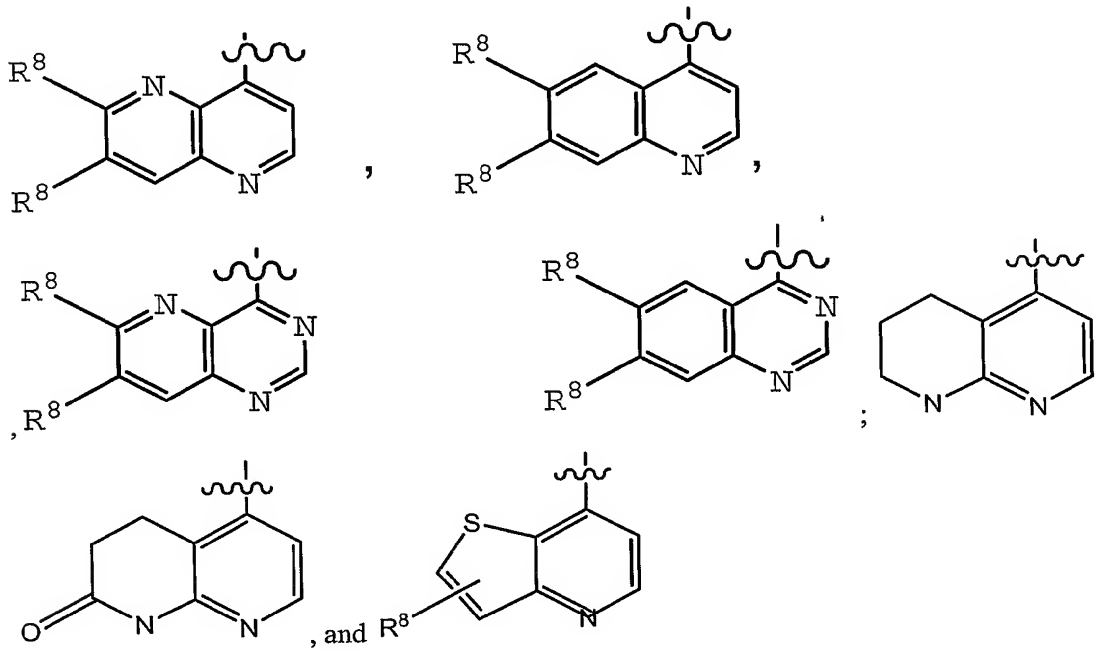
R^{8*} is one or more substituents independently selected at each occurrence from H, cyano, hydroxyl, halo, optionally substituted heterocyclyl, $-NR^aC(=O)NR^aR^5$, $NR^aC(=NR^b)-NR^5$, $NR^aC(=S)NR^aR^5$, $-OC(=O)NR^aR^5$, $-NR^aC(=O)OR^5$, $-NR^aC(=O)-R^5$, $R^5R^aN-O_2S-$, R^5O_2S-, $R^5O_2SR^aN-$, R^5R^aN-, alkyl, aminoalkyl, alkylaminoalkyl, alkoxyalkyl, phenylalkyl, heterocyclylalkyl, alkoxy, haloalkoxy, alkylaminoalkoxy, arylalkoxy, heterocyclylalkoxy, cycloalkylalkoxy, heterocyclyl(hydroxyalkoxy), cycloalkyl(hydroxyalkoxy), aryl(hydroxyalkoxy), alkoxyalkoxy, aryloxyalkoxy, heterocyclyloxyalkoxy, cycloalkyloxyalkoxy, aryloxy, heterocyclyloxy, and cycloalkyloxy; alternatively where R^{8a} comprises an NR^aR^5 moiety R^a and R^5, together with the nitrogen atom they are attached to, may optionally form a substituted or unsubstituted 4-6 membered ring;

p is 0, 1, 2, or 3; and

t is 0, 1 or 2;

wherein each alkyl, aryl, heteroaryl, cycloalkyl, alkenyl, alkynyl, heterocyclyl, and alkoxy moiety of any R, R^1, R^2, R^3, R^4, R^5, R^7, R^8, R^{8*}, and R^a is optionally independently substituted with one or more groups independently selected at each occurrence from halo, oxo, $-NR^aR^5$, $-OR^{5a}$, $-CO_2R^5$, $-C(=O)R^5$, $(C_1\text{-}C_6)$alkylamino, -NH-N=NH, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkynyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_1\text{-}C_6)$haloalkyl, di$(C_1\text{-}C_6)$alkylamino, $(C_1\text{-}C_6)$alkylamino-$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$hydroxyalkylamino, $(C_1\text{-}C_6)$alkylamino-$(C_1\text{-}C_6)$alkylamino, phenyl, heterocyclic, heteroaryl, $-(CR^3R^4)_p$alkyl-S(=O)-alkyl, and $-(CR^3R^4)_p$alkyl-$S(O)_2$-alkyl.

2. Compound of Claim 1, wherein R is selected from



wherein R^8 is independently selected at each occurrence from H, cyano, hydroxy, $-C(=O)NR^aR^{5a}$, 5-6 membered heterocyclyl, $-NR^aC(=O)-R^{5a}$, $R^{5a}R^aN\text{-}O_2S\text{-}$, $R^{5a}O_2SR^aN\text{-}$, $R^{5a}R^aN\text{-}$, $C_{1\text{-}6}$-alkyl, amino-$C_{1\text{-}6}$-alkyl, $C_{1\text{-}6}$-alkylamino-$C_{1\text{-}6}$-alkyl, alkoxy-$C_{1\text{-}6}$-alkyl, phenyl-$C_{1\text{-}6}$-alkyl, heterocyclyl-$C_{1\text{-}6}$-alkyl, $C_{1\text{-}6}$-alkoxy, halo-$C_{1\text{-}6}$-alkoxy, $C_{1\text{-}6}$-alkylamino-$C_{1\text{-}6}$-alkoxy, aryl-$C_{1\text{-}6}$-alkoxy, 5-6-membered heterocyclyl-$C_{1\text{-}6}$-alkoxy, $C_{3\text{-}6}$-cycloalkyl-$C_{1\text{-}6}$-alkoxy, 5-6-membered

heterocyclyl(hydroxyl-C_{1-6}-alkoxy), C_{3-6}-cycloalkyl(hydroxyl-C_{1-6}-alkoxy), phenyl(hydroxyl-C_{1-6}-alkoxy), C_{1-6}-alkoxy-C_{1-6}-alkoxy, phenyloxy-C_{1-6}-alkoxy, 5-6 membered heterocyclyloxy-C_{1-6}-alkoxy, C_{3-6}-cycloalkyloxy-C_{1-6}-alkoxy, phenyloxy, 5-6-membered heterocyclyloxy, and C_{3-6}-cycloalkyloxy;

wherein R^a is selected from H, C_{1-6}-alkyl, 5-6 membered heterocyclyl, phenyl, phenyl-C_{1-6}-alkyl, 5-6 membered heterocyclyl-C_{1-6}-alkyl, C_{3-6}-cycloalkyl, C_{3-6}-cycloalkyl-C_{1-6}-alkyl, C_{2-6}-alkenyl and C_{2-6}-alkynyl; and

wherein R^{5a} is selected from H, C_{1-6}-alkyl, C_{1-6}-haloalkyl, phenyl-C_{1-6}-alkyl, 5-6 membered heterocyclyl-C_{1-6}-alkyl, C_{3-6}-cycloalkyl-C_{1-6}-alkyl, phenyl, 5-6-membered heterocyclyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl and C_{3-6}-cycloalkyl;

and pharmaceutically acceptable salts thereof.

3. Compound of Claim 1 wherein R^8 is independently selected at each occurrence from H, cyano, aminocarbonyl, C_{1-3}-alkylaminocarbonyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-3}-alkylamino-C_{1-3}-alkoxy, 5-6 membered heterocyclyl-C_{1-3}-alkoxy, C_{4-6}-cycloalkyl-C_{1-3}-alkoxy, 5-6 membered heterocyclyl-C_{1-3}-(hydroxyalkoxy), C_{3-6}-cycloalkyl-C_{1-3}-(hydroxyalkoxy), C_{1-2}-alkoxy-C_{1-3}-alkoxy, phenyloxy-C_{1-3}alkoxy, 5-6 membered heterocyclyloxy-C_{1-3}-alkoxy, cycloalkyloxy-C_{1-3}-alkoxy, 5-6 membered heterocyclyloxy, and C_{3-6}-cycloalkyloxy; and pharmaceutically acceptable salts thereof.

4. Compound of Claim 1 wherein R^8 is independently selected from H, methyl, cyano, heterocyclic, heteroaryl, aminocarbonyl, methylaminocarbonyl, methoxy, dimethylaminopropoxy, 3-(morpholin-4-yl)propoxy, 3-(pyrrolidin-1-yl)propoxy, 2-hydroxy-3-(morpholin-4-yl)propoxy, 3-(1,2,4-triazol-1-yl)propoxy, 3-(4-methylpiperazin-1-yl)propoxy, 3-(piperidin-4-yl)propoxy, dimethylaminoethoxy and diethylaminoethoxy; and pharmaceutically acceptable salts thereof.

5. Compound of Claim 1 wherein R is selected from 6,7-dimethoxy-4-quinolinyl, 7-methoxy-4 quinonlinyl, 6-methoxy-7-(dimethylaminopropoxy)-4-quinolinyl, 6-methoxy-7-(3-(morpholin-4-yl)propoxy)-4-quinolinyl, 6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)-4-quinolinyl, 6-methoxy-7-(2-hydroxy-3-(morpholin-4-yl)propoxy)-4-quinolinyl, 6-methoxy-7-(3-(1,2,4-triazol-1-yl)propoxy)-4-quinolinyl, 6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)-4-quinolinyl, 6-methoxy-7-(3-(piperidin-4-yl)propoxy)-4-quinolinyl, 6,7-

dimethoxy-4-quinazolinyl and 6-methoxy-7-(dimethylaminopropoxy)-4-quinazolinyl; and pharmaceutically acceptable salts thereof.

6. Compound of Claim 1 wherein W is selected from substituted or unsubstituted phenyl, substituted or unsubstituted pyridyl, substituted or unsubstituted pyrimidinyl, substituted or unsubstituted pyridazinyl and substituted or unsubstituted pyrazinyl; and pharmaceutically acceptable salts thereof.

7. Compound of Claim 1 wherein W is substituted or unsubstituted phenyl; and pharmaceutically acceptable salts thereof.

8. Compound of Claim 1 wherein W is substituted or unsubstituted pyridyl; and pharmaceutically acceptable salts thereof.

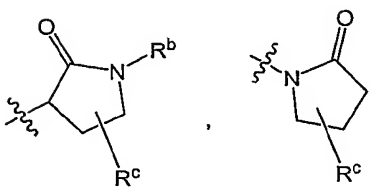
9. Compound of Claim 1 wherein X is O; and pharmaceutically acceptable salts thereof.

10. Compound of Claim 1 wherein Y is selected from -NHC(=O)-, –NHC(=O)-$(CH_2)_p$-, –NH-$(CH_2)_p$-, and –NH-$(CH_2)_pC(=O)$-; and wherein p is 0 or 1; and pharmaceutically acceptable salts thereof.

11. Compound of Claim 1 wherein Y is -NHC(=O)-; and pharmaceutically acceptable salts thereof.

12. Compound of Claim 1 wherein p is 1; and pharmaceutically acceptable salts thereof.

13. Compound of Claim 1 wherein R^1 is selected from



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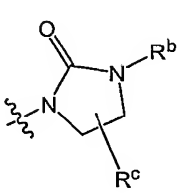

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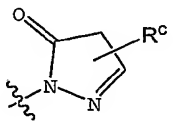

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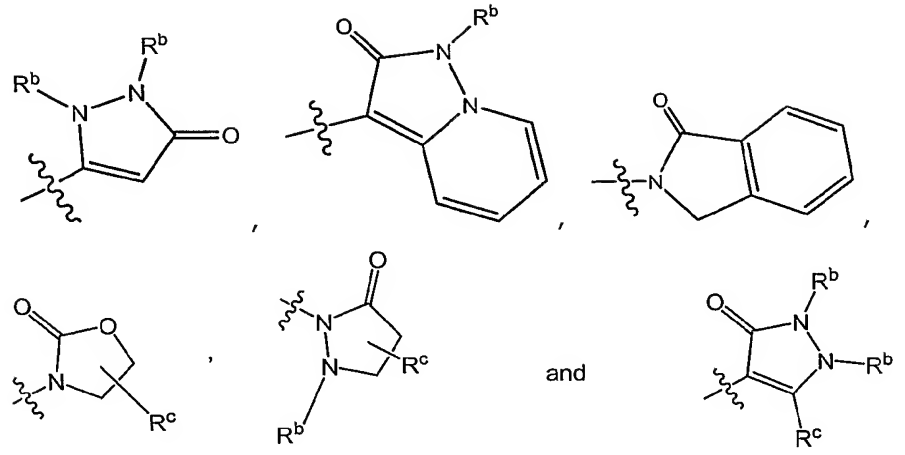


wherein R^b is independently selected at each occurrence from H, optionally substituted arylalkyl, optionally substituted 5-6-membered heterocyclyl-C_{1-3} alkyl, optionally substituted C_{1-6}-alkyl, optionally substituted 5-6 membered heterocyclyl, optionally substituted C_{6-10} ary, optionally substituted C_{6-10} heteroaryl, optionally substituted C_{3-6} cycloalkyl, and $R^aR^{5a}N$-C_{1-3}alkyl;

wherein R^c is one or more substituents selected from H, methyl, isopropyl, tert-butyl, bromo, fluoro, hydroxyl, $R^{5a}R^aN$-, $R^{5a}R^aN$-C_{1-3} alkyl, methoxymethyl, methoxyethyl, methylthiomethyl, piperidin-1-ylmethyl, pyrrolidin-1-ylmethyl, optionally substituted phenyl, optionally substituted pyridyl, optionally substituted thienyl, and optionally substituted benzyl; wherein R^a is selected from H, methyl, ethyl, isopropyl, butyl, sec-butyl, isobutyl, phenyl, and phenylmethyl; and wherein R^{5a} is selected from H, methyl, ethyl, isopropyl, butyl, sec-butyl, isobutyl, phenylmethyl, optionally substituted 5-6 membered heterocyclyl-C_{1-2}-alkyl, optionally substituted phenyl, and optionally substituted 5-6-membered heterocyclyl; C_{6-10} aryl, nitrile, $-C(=O)OR^{5a}$, $-C(=O)NR^{5a}R^a$, $-C(=O)R^{5a}$ and optionally substituted heteroraryl

wherein R^a is selected from H, C_{1-6}-alkyl, optionally substituted 5-6 membered heterocyclyl, optionally substituted phenyl, optionally substituted phenyl-C_{1-6}-alkyl, optionally substituted 5-6 membered heterocyclyl-C_{1-6}-alkyl, C_{3-6}-cycloalkyl, C_{3-6}-cycloalkyl-C_{1-6}-alkyl, C_{2-6}-alkenyl and C_{2-6}-alkynyl; and

wherein R^{5a} is selected from H, C_{1-6}-alkyl, C_{1-6}-haloalkyl, phenyl-C_{1-6}-alkyl, 5-6 membered heterocyclyl-C_{1-6}-alkyl, C_{3-6}-cycloalkyl-C_{1-6}-alkyl, $R^aC(=O)$-, optionally substituted phenyl, optionally substituted 5-6-membered heterocyclyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl and C_{3-6}-cycloalkyl;

or wherein two adjacent R^c substituents, two adjacent R^b substituents or R^c together with an adjacent R^b together form an optionally substituted fused ring; or wherein two R^c substituents, together form an optionally substituted spiro ring;

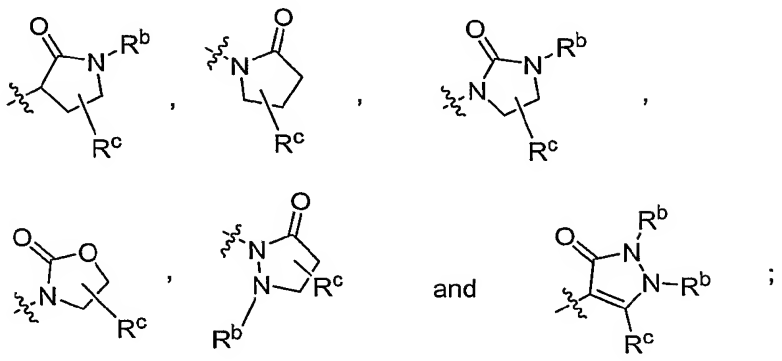
and pharmaceutically acceptable salts thereof.

14. Compound of Claim 13 wherein

R^b is selected from H, optionally substituted benzyl, C_{1-3} alkylaryl, C_{1-3} alkylheteroaryl, methyl, ethyl, isopropyl, butyl, sec-butyl, isobutyl, methoxymethyl,, -(C_{1-6})alkyl,2-hydroxy 2-methylbutyl, 2-hydroxy-2-methylpropyl, 2-hydroxypropyl, 1-(1-hydroxycyclopropyl)methyl,, ethylaminomethyl, piperidin-1-ylmethyl, pyrrolidin-1-ylmethyl, pyridyl, thienyl, optionally substituted phenyl,1-naphthy, nitrile, $-C(=O)OR^{5a}$, $-C(=O)NR^{5a}R^a$, and $-C(=O)R^{5a}$;

R^c is one or more substituents selected from H, methyl, isopropyl, tert-butyl, bromo, fluoro, hydroxyl, $R^{5a}R^aN$-, $R^{5a}R^aN$-C_{1-3} alkyl, methoxymethyl, methoxyethyl, methylthiomethyl, piperidin-1-ylmethyl, pyrrolidin-1-ylmethyl, optionally substituted phenyl, optionally substituted pyridyl, optionally substituted thienyl, and optionally substituted benzyl; wherein R^a is selected from H, methyl, ethyl, isopropyl, butyl, sec-butyl, isobutyl, phenyl, and phenylmethyl; and wherein R^{5a} is selected from H, methyl, ethyl, isopropyl, butyl, sec-butyl, isobutyl, phenylmethyl, optionally substituted 5-6 membered heterocyclyl-C_{1-2}-alkyl, optionally substituted phenyl, and optionally substituted 5-6-membered heterocyclyl; C_{6-10} aryl, nitrile, $-C(=O)OR^{5a}$, $-C(=O)NR^{5a}R^a$, $-C(=O)R^{5a}$ and optionally substituted heteroraryl; or wherein two R^c substituents, two R^b substituents or R^c together with R^b together form an optionally substituted fused phenyl ring; or wherein two R^c substituents bound to the same atom, together form an optionally substituted 3-6 membered spiro ring; and pharmaceutically acceptable salts solvates and N-Oxides thereof.

15. Compound of Claim 1 wherein R^1 is selected from



wherein R^b is independently selected at each occurrence from H, optionally substituted phenyl-C_{1-3} alkyl, optionally substituted 5-6-membered heterocyclyl-C_{1-3} alkyl, optionally substituted C_{1-6}-alkyl, optionally substituted 5-6 membered heterocyclyl, optionally substituted C_{6-10} ary, optionally substitutedC_{6-10}heteroaryl,, optionally substituted C_{3-6} cycloalkyl, 2-oxo-propyl, 2-fluoropropyl 2-azidopropyl, and $R^aR^{5a}N$-C_{1-3}alkyl;

wherein R^c is one or more substituents selected from H, halo, hydroxyl, $R^{5a}R^aN$-, $R^{5a}R^aN$-C_{1-3} alkyl, C_{1-3} alkoxy-C_{1-3} alkyl, C_{1-3} alkylthio-C_{1-3} alkyl, optionally substituted phenyl-C_{1-3} alkyl, optionally substituted 5-6-membered heterocyclyl-C_{1-3} alkyl, optionally substituted C_{1-6}-alkyl, optionally substituted 5-6 membered heterocyclyl, -C_{1-3} alkyl-NR^a-C(=O)-OR^5, optionally substituted C_{6-10} aryl; nitrile, -C(=O)OR^{5a}, -C(=O)$NR^{5a}R^a$, -C(=O)R^{5a} and optionally substituted heteroraryl;

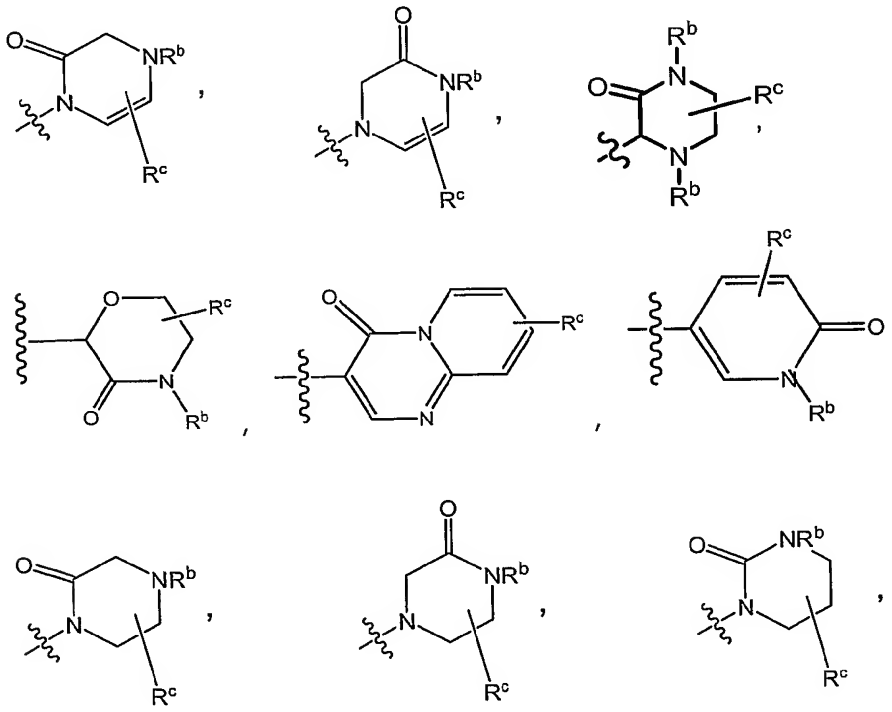
wherein R^a is selected from H, C_{1-6}-alkyl, optionally substituted 5-6 membered heterocyclyl, optionally substituted phenyl, optionally substituted phenyl-C_{1-6}-alkyl, optionally substituted 5-6 membered heterocyclyl-C_{1-6}-alkyl, C_{3-6}-cycloalkyl, C_{3-6}-cycloalkyl-C_{1-6}-alkyl, C_{2-6}-alkenyl and C_{2-6}-alkynyl; and

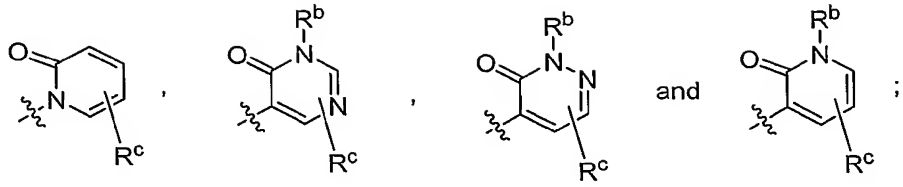
wherein R^{5a} is selected from H, C_{1-6}-alkyl, C_{1-6}-haloalkyl, phenyl-C_{1-6}-alkyl, 5-6 membered heterocyclyl-C_{1-6}-alkyl, C_{3-6}-cycloalkyl-C_{1-6}-alkyl, $R^aC(=O)$-, optionally substituted phenyl, optionally substituted 5-6-membered heterocyclyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl and C_{3-6}-cycloalkyl;

or wherein two adjacent R^c substituents, two adjacent R^b substituents or R^c together with an adjacent R^b together form an optionally substituted fused ring; or wherein two R^c substituents bound to the same atom, together form an optionally substituted spiro ring; and pharmaceutically acceptable salts solvates and N-Oxodes thereof.

16. A Compound of Claim 15 wherein R^b is selected from H, optionally substituted benzyl, methyl, ethyl, isopropyl, butyl, sec-butyl, isobutyl, 3-hydroxypropyl, methoxymethyl, methoxyethyl, 2-hydroxy-2-methylpropyl,2-oxopropyl, 2-azidopropyl,, 2-fluoropropyl,, 2-hydroxypropyl, , 2-hydroxy-3-aminoproply,.2-methoxypropyl,, 2-aminoproply,, 1(1-hydroxycycloproplyl)methyl, ethylaminomethyl, piperidin-1-ylmethyl, pyrrolidin-1-ylmethyl, pyridyl, thienyl, optionally substituted phenyl, and 1-naphthyl; wherein R^c is one or more substituents selected from H, methyl, isopropyl, tert-butyl, bromo, fluoro, hydroxyl, $R^{5a}R^aN$-, $R^{5a}R^aN$-C_{1-3} alkyl, methoxymethyl, methoxyethyl, methylthiomethyl, piperidin-1-ylmethyl, pyrrolidin-1-ylmethyl, optionally substituted phenyl, optionally substituted heteroaryl, and optionally substituted benzyl; wherein R^a is selected from H, methyl, ethyl, isopropyl, butyl, sec-butyl, isobutyl, phenyl, and phenylmethyl; and wherein R^{5a} is selected from H, methyl, ethyl, isopropyl, butyl, sec-butyl, isobutyl, phenylmethyl, optionally substituted 5-6 membered heterocyclyl-C_{1-2}-alkyl, optionally substituted phenyl, and optionally substituted 5-6-membered heterocyclyl; or wherein two R^c substituents, two R^b substituents or R^c together with R^b together form an optionally substituted fused phenyl ring; or wherein two R^c substituents, together form an optionally substituted 3-6 membered spiro ring; and pharmaceutically acceptable salts thereof.

17. Compound of Claim 1 wherein R^1 is selected from





wherein R^b is independently selected at each occurrence from H, optionally substituted phenyl-C_{1-3} alkyl, optionally substituted 5-6-membered heterocyclyl-C_{1-3} alkyl, optionally substituted C_{1-6}-alkyl, optionally substituted 5-6 membered heterocyclyl, optionally substituted C_{6-10} aryl, optionally substituted C_{6-10} heteroaryl, optionally substituted C_{3-6} cycloalkyl, and $R^aR^{5a}N$-C_{1-3}alkyl;

wherein R^c is one or more substituents selected from H, halo, hydroxyl, $R^{5a}R^aN$-, $R^{5a}R^aN$-C_{1-3} alkyl, C_{1-3} alkoxy-C_{1-3} alkyl, C_{1-3} alkylthio-C_{1-3} alkyl, optionally substituted phenyl-C_{1-3} alkyl, optionally substituted 5-6-membered heterocyclyl-C_{1-3} alkyl, optionally substituted C_{1-6}-alkyl, optionally substituted 5-6 membered heterocyclyl, -C_{1-3} alkyl-NR^a-C(=O)-OR^5, optionally substituted C_{6-10} aryl; nitrile, -C(=O)OR^{5a}, -C(=O)$NR^{5a}R^a$, -C(=O)R^{5a} and optionally substituted heteroraryl;

wherein R^a is selected from H, C_{1-6}-alkyl, optionally substituted 5-6 membered heterocyclyl, optionally substituted phenyl, optionally substituted phenyl-C_{1-6}-alkyl, optionally substituted 5-6 membered heterocyclyl-C_{1-6}-alkyl, C_{3-6}-cycloalkyl, C_{3-6}-cycloalkyl-C_{1-6}-alkyl, C_{2-6}-alkenyl and C_{2-6}-alkynyl; and

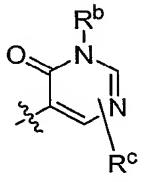
wherein R^{5a} is selected from H, C_{1-6}-alkyl, C_{1-6}-haloalkyl, phenyl-C_{1-6}-alkyl, 5-6 membered heterocyclyl-C_{1-6}-alkyl, C_{3-6}-cycloalkyl-C_{1-6}-alkyl, $R^aC(=O)$-, optionally substituted phenyl, optionally substituted 5-6-membered heterocyclyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl and C_{3-6}-cycloalkyl;

or wherein two adjacent R^c substituents, two adjacent R^b substituents or R^c together with an adjacent R^b together form an optionally substituted fused ring; or wherein two R^c substituents, together form an optionally substituted spiro ring; and pharmaceutically acceptable salts thereof.

18. Compound of Claim 17 wherein R^b is selected from H, optionally substituted benzyl, methyl, ethyl, isopropyl, butyl, sec-butyl, isobutyl, hydroxymethyl, methoxymethyl, methoxyethyl, 2-hydroxy-2-methylpropyl, methylaminomethyl, ethylaminomethyl, piperidin-1-ylmethyl, pyrrolidin-1-ylmethyl, pyridyl, thienyl, optionally substituted phenyl, and 1-naphthyl; wherein R^c is one or more substituents selected from H, methyl, isopropyl, tert-butyl,

bromo, fluoro, hydroxyl, $R^{5a}R^aN$-, $R^{5a}R^aN$-C_{1-3} alkyl, methoxymethyl, methoxyethyl, methylthiomethyl, piperidin-1-ylmethyl, pyrrolidin-1-ylmethyl, optionally substituted phenyl, optionally substituted pyridyl, optionally substituted thienyl, and optionally substituted benzyl; wherein R^a is selected from H, methyl, ethyl, isopropyl, butyl, sec-butyl, isobutyl, phenyl, and phenylmethyl; and wherein R^{5a} is selected from H, methyl, ethyl, isopropyl, butyl, sec-butyl, isobutyl, phenylmethyl, optionally substituted 5-6 membered heterocyclyl-C_{1-2}-alkyl, optionally substituted phenyl, and optionally substituted 5-6-membered heterocyclyl; or wherein two R^c substituents, two R^b substituents or R^c together with R^b together form an optionally substituted fused phenyl ring; or wherein two R^c substituents, together form an optionally substituted 3-6 membered spiro ring; and pharmaceutically acceptable salts thereof.

19. Compound of Claim 1 wherein R^1 is selected from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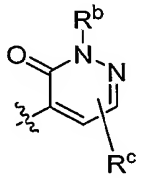
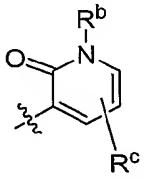

and

;

wherein R^b is independently selected at each occurrence from H, optionally substituted phenyl-C_{1-3} alkyl, optionally substituted 5-6-membered heterocyclyl-C_{1-3} alkyl, optionally substituted C_{1-6}-alkyl, optionally substituted 5-6 membered heterocyclyl, optionally substituted C_{6-10} ary, and $R^aR^{5a}N$-C_{1-3}alkyl;

wherein R^c is one or more substituents selected from H, halo, hydroxyl, $R^{5a}R^aN$-, $R^{5a}R^aN$-C_{1-3} alkyl, C_{1-3} alkoxy-C_{1-3} alkyl, C_{1-3} alkylthio-C_{1-3} alkyl, optionally substituted phenyl-C_{1-3} alkyl, optionally substituted 5-6-membered heterocyclyl-C_{1-3} alkyl, optionally substituted C_{1-6}-alkyl, optionally substituted 5-6 membered heterocyclyl, -C_{1-3} alkyl-NR^a-C(=O)-OR^5, optionally substituted C_{6-10} aryl; and optionally substituted heteroraryl;

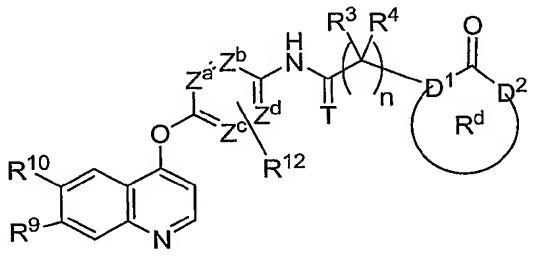
wherein R^a is selected from H, C_{1-6}-alkyl, optionally substituted 5-6 membered heterocyclyl, optionally substituted phenyl, optionally substituted phenyl-C_{1-6}-alkyl, optionally substituted 5-6 membered heterocyclyl-C_{1-6}-alkyl, C_{3-6}-cycloalkyl, C_{3-6}-cycloalkyl-C_{1-6}-alkyl, C_{2-6}-alkenyl and C_{2-6}-alkynyl; and

wherein R^{5a} is selected from H, C_{1-6}-alkyl, C_{1-6}-haloalkyl, phenyl-C_{1-6}-alkyl, 5-6 membered heterocyclyl-C_{1-6}-alkyl, C_{3-6}-cycloalkyl-C_{1-6}-alkyl, $R^aC(=O)$-, optionally substituted phenyl, optionally substituted 5-6-membered heterocyclyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl and C_{3-6}-cycloalkyl;

or wherein two adjacent R^c substituents, two adjacent R^b substituents or R^c together with an adjacent R^b together form an optionally substituted fused ring; or wherein two R^c substituents, together form an optionally substituted spiro ring; and pharmaceutically acceptable salts thereof.

20. Compound of Claim 19 wherein R^b is selected from H, optionally substituted benzyl, methyl, ethyl, isopropyl, butyl, sec-butyl, isobutyl, hydroxymethyl, methoxymethyl, methoxyethyl, 2-hydroxy-2-methylpropyl, methylaminomethyl, ethylaminomethyl, piperidin-1-ylmethyl, pyrrolidin-1-ylmethyl, pyridyl, thienyl, optionally substituted phenyl, and 1-naphthyl; wherein R^c is one or more substituents selected from H, methyl, isopropyl, tert-butyl, bromo, fluoro, hydroxyl, $R^{5a}R^aN$-, $R^{5a}R^aN$-C_{1-3} alkyl, methoxymethyl, methoxyethyl, methylthiomethyl, piperidin-1-ylmethyl, pyrrolidin-1-ylmethyl, optionally substituted phenyl, optionally substituted pyridyl, optionally substituted thienyl, and optionally substituted benzyl; wherein R^a is selected from H, methyl, ethyl, isopropyl, butyl, sec-butyl, isobutyl, phenyl, and phenylmethyl; and wherein R^{5a} is selected from H, methyl, ethyl, isopropyl, butyl, sec-butyl, isobutyl, phenylmethyl, optionally substituted 5-6 membered heterocyclyl-C_{1-2}-alkyl, optionally substituted phenyl, and optionally substituted 5-6-membered heterocyclyl; or wherein two R^c substituents, two R^b substituents or R^c together with R^b together form an optionally substituted fused phenyl ring; or wherein two R^c substituents, together form an optionally substituted 3-6 membered spiro ring; and pharmaceutically acceptable salts thereof.

21. Compound of Claim 1,



II

enantiomers, diastereomers, salts, solvates and N-Oxides thereof

wherein T is O or S;

wherein R^3 and R^4 is each independently selected from H, C_{1-2}-alkyl, phenyl, 5-6-membered heterocyclyl, phenyl-C_{1-2}-alkyl, 5-6-membered heterocyclyl- C_{1-2}-alkyl, C_{3-6}-cycloalkyl, and C_{3-6}-cycloalkyl-C_{1-2}-alkyl; alternatively R^3 and R^4, together with the atom they are attached to, form an optionally substituted 3-6 membered ring;

wherein R^9 and R^{10} is independently selected from H, cyano, hydroxy, -C(=O)NR^aR^{5a}, 5-6 membered heterocyclyl, -$NR^aC(=O)$-R^{5a}, $R^{5a}R^aN$-O_2S-, $R^{5a}O_2SR^aN$-, $R^{5a}R^aN$-, C_{1-6}-alkyl, amino-C_{1-6}-alkyl, C_{1-6}-alkylamino-C_{1-6}-alkyl, alkoxy-C_{1-6}-alkyl, hydroxy, aryl-C_{1-6}-alkyl, heterocyclyl-C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, C_{1-6}-alkylamino-C_{1-6}-alkoxy, aryl-C_{1-6}-alkoxy, 5-6-membered heterocyclyl, -C_{1-6}alkoxy, C_{3-6}-cycloalkyl-C_{1-6}-alkoxy, 5-6-membered heterocyclyl(hydroxyl-C_{1-6}-alkoxy), C_{3-6}-cycloalkyl(hydroxyl-C_{1-6}-alkoxy), phenyl(hydroxyl-C_{1-6}-alkoxy), C_{1-6}-alkoxy-C_{1-6}-alkoxy, phenyloxy-C_{1-6}-alkoxy, 5-6 membered heterocyclyloxy-C_{1-6}-alkoxy, C_{3-6}-cycloalkyloxy-C_{1-6}-alkoxy, phenyloxy, 5-6-membered heterocyclyloxy, and C_{3-6}-cycloalkyloxy;

wherein each of Z^a, Z^b, Z^c and Z^d is independently selected from N or CH; provided no more than 2 of Z^a, Z^b, Z^c and Z^d are N;

wherein n is 0, 1, 2 or 3;

wherein D^1 is selected from N or CR^{11};

wherein D^2 is selected from NR^{13}, O, or CHR^{11}; provided either D^1 is N or D^2 is NR^{13};

wherein ring R^d including  forms an optionally substituted optionally benzo-fused 4-7 membered heterocyclic moiety,

wherein R^{11} is selected from H, halo, C_{1-4}-alkyl, C_{1-4}-haloalkyl, C_{1-4}-hydroxyalkyl, -NH_2, -OR^{12}, alkoxycarbonyl, -CO_2H, -$CONR^3R^{5a}$, (C_1-C_3)alkylamino, di(C_1-C_6)alkylamino, (C_1-C_3)hydroxyalkylamino, (C_1-C_3)alkylamino-(C_1-C_3)alkylamino, C_{1-3}-alkoxy-C_{1-3}-alkyl, C_{1-3}-alkylamino-C_{1-3}-alkyl, C_{1-3}-alkylthio-C_{1-3}-alkyl, optionally substituted phenyl-C_{1-3}-alkyl, 5-6 membered heterocyclyl-C_{1-3}-alkyl, C_{3-6}-cycloalkyl-C_{1-3}-alkyl, optionally substituted phenyl, optionally substituted 5-6 membered heterocyclyl, and C_{3-6}-cycloalkyl;

wherein R^a is selected from H, alkyl, heterocyclyl, aryl, arylalkyl, heterocyclylalkyl, cycloalkyl, cycloalkylalkyl, alkenyl and alkynyl;

wherein R^{5a} is selected from H, alkyl, haloalkyl, arylalkyl, heterocyclylalkyl, cycloalkylalkyl, aryl, heterocyclyl, alkenyl, alkynyl and cycloalkyl;

wherein R^{12} is selected from H, halo, C_{1-2}-alkyl and methoxy;

wherein R^{13} is selected from H, alkyl, haloalkyl, optionally substituted phenylalkyl, optionally substituted 5-10 membered heterocyclylalkyl, cycloalkylalkyl, optionally substituted phenyl or naphthyl, optionally substituted 5-10 membered heterocyclyl and cycloalkyl;

and pharmaceutically acceptable salts thereof.

22. Compound of Claim 21 wherein R^9 and R^{10} are independently selected from H, cyano, aminocarbonyl, C_{1-3}-alkylaminocarbonyl, C_{1-3}-alkylamino-C_{1-3}-alkoxy, 5-6 membered heterocyclyl, -C_{1-3}-alkoxy, hydroxy C_{4-6}-cycloalkyl-C_{1-3}-alkoxy, 5-6 membered heterocyclyl-C_{1-3}-(hydroxyalkoxy), C_{3-6}-cycloalkyl-C_{1-3}-(hydroxyalkoxy), C_{1-2}-alkoxy-C_{1-3}-alkoxy, phenyloxy-C_{1-3}alkoxy, 5-6 membered heterocyclyloxy-C_{1-3}-alkoxy, cycloalkyloxy-C_{1-3}-alkoxy, 5-6 membered heterocyclyloxy, and C_{3-6}-cycloalkyloxy; and pharmaceutically acceptable salts solvates and N-Oxides thereof.

23. Compound of Claim 21 wherein R^9 is independently selected from H, methyl, cyano, aminocarbonyl, methylaminocarbonyl, methoxy, hydroxy, dimethylaminopropoxy, 3-(morpholin-4-yl)propoxy, 3-(pyrrolidin-1-yl)propoxy, 2-hydroxy-3-(morpholin-4-yl)propoxy, 3-(1,2,4-triazol-1-yl)propoxy, 3-(4-methylpiperazin-1-yl)propoxy, 3-(piperidin-4-yl)propoxy, dimethylaminoethoxy, 1-morpholinyl, 1-piperazinyl, 4-methylpiperazinyl, pyrolidinyl,, 3-aminopyrolidnyl, diethylaminoethoxy; and pharmaceutically acceptable salts thereof.

24. Compound of Claim 21 wherein

R^{10} is H or alkoxy; and

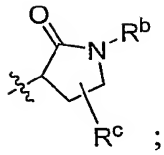
R^9 isalkoxy; or heterocyclyl and pharmaceutically acceptable salts solvates and N-Oxides thereof.

25. Compound of Claim 21 wherein Z^a is CH; wherein Z^b is CH; wherein Z^c is CF; and wherein Z^d is CH; and pharmaceutically acceptable salts thereof.

26. Compound of Claim 21 wherein Z^a is N; wherein Z^a is CH; wherein Z^c is CH; wherein Z^d is CH; and wherein R^{12} is H; and pharmaceutically acceptable salts thereof.

27. Compound of Claim 21 wherein Z^a is CH; wherein Z^b is N; wherein Z^c is CH; wherein Z^d is CH; and wherein R^{12} is H; and pharmaceutically acceptable salts thereof.

28. Compound of Claim 15 wherein Z^a is CH; wherein Z^b is N; wherein Z^c is CH; wherein Z^d is N; and wherein R^{12} is H; and pharmaceutically acceptable salts thereof.

29. Compound of Claim 21 wherein R^d is  ;

wherein R^b is selected from H, optionally substituted phenyl-C_{1-3} alkyl, optionally substituted 5-6-membered heterocyclyl-C_{1-3} alkyl, optionally substituted C_{1-6}-alkyl, optionally substituted 5-6 membered heterocyclyl, and optionally substituted C_{6-10} aryl;

wherein R^c is one or more substituents selected from H, halo, hydroxyl, $R^{5a}R^aN$-, $R^{5a}R^aN$-C_{1-3} alkyl, C_{1-3} alkoxy-C_{1-3} alkyl, C_{1-3} alkylthio-C_{1-3} alkyl, optionally substituted phenyl-C_{1-3} alkyl, optionally substituted 5-6-membered heterocyclyl-C_{1-3} alkyl, optionally substituted C_{1-6}-alkyl, optionally substituted 5-6 membered heterocyclyl, and optionally substituted C_{6-10} aryl;

wherein R^a is selected from H, C_{1-6}-alkyl, optionally substituted 5-6 membered heterocyclyl, optionally substituted phenyl, optionally substituted phenyl-C_{1-6}-alkyl, optionally substituted 5-6 membered heterocyclyl-C_{1-6}-alkyl, C_{3-6}-cycloalkyl, C_{3-6}-cycloalkyl-C_{1-6}-alkyl, C_{2-6}-alkenyl and C_{2-6}-alkynyl; and

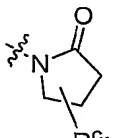
wherein R^{5a} is selected from H, C_{1-6}-alkyl, C_{1-6}-haloalkyl, phenyl-C_{1-6}-alkyl, 5-6 membered heterocyclyl-C_{1-6}-alkyl, C_{3-6}-cycloalkyl-C_{1-6}-alkyl, $R^aC(=O)$-, optionally substituted phenyl, optionally substituted 5-6-membered heterocyclyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl and C_{3-6}-cycloalkyl;

or wherein two adjacent R^c substituents, two adjacent R^b substituents or R^c together with an adjacent R^b together form an optionally substituted fused phenyl ring; or wherein two R^c substituents, together form an optionally substituted spiro ring;

and pharmaceutically acceptable salts thereof.

30. Compound of Claim 29 wherein R^b is selected from H, optionally substituted benzyl, methyl, ethyl, isopropyl, butyl, sec-butyl, isobutyl, hydroxymethyl, methoxymethyl, methoxyethyl, 2-hydroxy-2-methylpropyl, methylaminomethyl, ethylaminomethyl, piperidin-1-ylmethyl, pyrrolidin-1-ylmethyl, pyridyl, thienyl, optionally substituted phenyl, and 1-naphthyl; wherein R^c is one or more substituents selected from H, methyl, isopropyl, tert-butyl, bromo, fluoro, hydroxyl, $R^{5a}R^aN$-, $R^{5a}R^aN$-C_{1-3} alkyl, methoxymethyl, methoxyethyl, methylthiomethyl, piperidin-1-ylmethyl, pyrrolidin-1-ylmethyl, optionally substituted phenyl, optionally substituted pyridyl, optionally substituted thienyl, and optionally substituted benzyl; wherein R^a is selected from H, methyl, ethyl, isopropyl, butyl, sec-butyl, isobutyl, phenyl, and phenylmethyl; and wherein R^{5a} is selected from H, methyl, ethyl, isopropyl, butyl, sec-butyl,

isobutyl, phenylmethyl, optionally substituted 5-6 membered heterocyclyl-C_{1-2}-alkyl, optionally substituted phenyl, and optionally substituted 5-6-membered heterocyclyl; or wherein two R^c substituents, two R^b substituents or R^c together with R^b together form an optionally substituted fused phenyl ring; or wherein two R^c substituents bound to the same atom, together form an optionally substituted 3-6 membered spiro ring; and pharmaceutically acceptable salts thereof.

31. Compound of Claim 21 wherein R^d is  ; wherein R^c is one or more substituents selected from H, halo, hydroxyl, $R^{5a}R^aN$-, $R^{5a}R^aN$-C_{1-3} alkyl, C_{1-3} alkoxy-C_{1-3} alkyl, C_{1-3} alkylthio-C_{1-3} alkyl, optionally substituted phenyl-C_{1-3} alkyl, optionally substituted 5-6-membered heterocyclyl-C_{1-3} alkyl, optionally substituted C_{1-6}-alkyl, optionally substituted 5-6 membered heterocyclyl, and optionally substituted C_{6-10} aryl; wherein two R^c groups bound the same atome my combine to form a C_{3-6} spiro ring

wherein R^a is selected from H, C_{1-6}-alkyl, optionally substituted 5-6 membered heterocyclyl, optionally substituted phenyl, optionally substituted phenyl-C_{1-6}-alkyl, optionally substituted 5-6 membered heterocyclyl-C_{1-6}-alkyl, C_{3-6}-cycloalkyl, C_{3-6}-cycloalkyl-C_{1-6}-alkyl, C_{2-6}-alkenyl and C_{2-6}-alkynyl; and

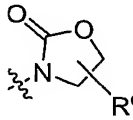
wherein R^{5a} is selected from H, C_{1-6}-alkyl, C_{1-6}-haloalkyl, phenyl-C_{1-6}-alkyl, 5-6 membered heterocyclyl-C_{1-6}-alkyl, C_{3-6}-cycloalkyl-C_{1-6}-alkyl, $R^aC(=O)$-, optionally substituted phenyl, optionally substituted 5-6-membered heterocyclyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl and C_{3-6}-cycloalkyl;

or wherein two adjacent R^c substituents, two adjacent R^b substituents or R^c together with an adjacent R^b together form an optionally substituted fused phenyl ring; or wherein two R^c substituents, together form an optionally substituted spiro ring;

and pharmaceutically acceptable salts thereof.

32. Compound of Claim 31 wherein R^c is one or more substituents selected from H, methyl, isopropyl, tert-butyl, bromo, fluoro, hydroxyl, $R^{5a}R^aN$-, $R^{5a}R^aN$-C_{1-3} alkyl, methoxymethyl, methoxyethyl, methylthiomethyl, piperidin-1-ylmethyl, pyrrolidin-1-ylmethyl, optionally substituted phenyl, optionally substituted pyridyl, optionally substituted thienyl, and optionally substituted benzyl; wherein R^a is selected from H, methyl, ethyl, isopropyl, butyl, sec-butyl, isobutyl, phenyl, and phenylmethyl; and wherein R^{5a} is selected from H, methyl,

ethyl, isopropyl, butyl, sec-butyl, isobutyl, phenylmethyl, optionally substituted 5-6 membered heterocyclyl-C_{1-2}-alkyl, optionally substituted phenyl, and optionally substituted 5-6-membered heterocyclyl; or wherein two R^c substituents, two R^b substituents or R^c together with R^b together form an optionally substituted fused phenyl ring; or wherein two R^c substituents, together form an optionally substituted 3-6 membered spiro ring; and pharmaceutically acceptable salts thereof.

33. Compound of Claim 21 wherein R^d is  ; wherein R^c is one or more substituents selected from H, halo, hydroxyl, $R^{5a}R^aN$-, $R^{5a}R^aN$-C_{1-3} alkyl, C_{1-3} alkoxy-C_{1-3} alkyl, C_{1-3} alkylthio-C_{1-3} alkyl, optionally substituted phenyl-C_{1-3} alkyl, optionally substituted 5-6-membered heterocyclyl-C_{1-3} alkyl, optionally substituted C_{1-6}-alkyl, optionally substituted 5-6 membered heterocyclyl, and optionally substituted C_{6-10} aryl; wherein two R^c groups bound to the same atom may combine to form a C_{3-6} spiro ring;

wherein R^a is selected from H, C_{1-6}-alkyl, optionally substituted 5-6 membered heterocyclyl, optionally substituted phenyl, optionally substituted phenyl-C_{1-6}-alkyl, optionally substituted 5-6 membered heterocyclyl-C_{1-6}-alkyl, C_{3-6}-cycloalkyl, C_{3-6}-cycloalkyl-C_{1-6}-alkyl, C_{2-6}-alkenyl and C_{2-6}-alkynyl; and

wherein R^{5a} is selected from H, C_{1-6}-alkyl, C_{1-6}-haloalkyl, phenyl-C_{1-6}-alkyl, 5-6 membered heterocyclyl-C_{1-6}-alkyl, C_{3-6}-cycloalkyl-C_{1-6}-alkyl, $R^aC(=O)$-, optionally substituted phenyl, optionally substituted 5-6-membered heterocyclyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl and C_{3-6}-cycloalkyl;

or wherein two adjacent R^c substituents, two adjacent R^b substituents or R^c together with an adjacent R^b together form an optionally substituted fused phenyl ring; or wherein two R^c substituents, together form an optionally substituted spiro ring;

and pharmaceutically acceptable salts thereof.

34. Compound of Claim 31 wherein R^c is one or more substituents selected from H, methyl, isopropyl, tert-butyl, bromo, fluoro, hydroxyl, $R^{5a}R^aN$-, $R^{5a}R^aN$-C_{1-3} alkyl, methoxymethyl, methoxyethyl, methylthiomethyl, piperidin-1-ylmethyl, pyrrolidin-1-ylmethyl, optionally substituted phenyl, optionally substituted pyridyl, optionally substituted thienyl, and optionally substituted benzyl; wherein R^a is selected from H, methyl, ethyl, isopropyl, butyl, sec-butyl, isobutyl, phenyl, and phenylmethyl; and wherein R^{5a} is selected from H, methyl, ethyl, isopropyl, butyl, sec-butyl, isobutyl, phenylmethyl, optionally substituted 5-6 membered